Article

Immunohistochemical and electrophysiological investigation of E/I balance alterations in animal models of frontotemporal dementia

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Ageing and dementia

The neurological consequences and pathological implications of bilingualism

Unique Code: TP001019

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Topic: Ageing and dementia

Introduction: In recent years, there has been a rise in the number of people able to speak two or more languages. This has been paralleled by an increase in research related to bilingualism. Despite this, many of the neurological consequences and pathological implications of bilingualism are still subject to discussion. This review aims to evaluate the neurological and neuroanatomical changes related to language and to the acquisition of a second language. The review also explores how learning a second language can alter one's susceptibility to and the progression of certain cerebral pathologies and age-related cognitive decline.

Methods: A literature search was conducted on the Medline, Embase and Web of Science databases. 137 articles regarding the neuroanatomical or pathological implications of bilingualism were included for review. Full text review deemed an article relevant for inclusion if it provided information on bilingualism relating either to neurology, neuroanatomy or pathological implications.

Approach for statistical analysis:
Qualitative analysis was conducted in the form of a narrative synthesis construction and focused on bilingual neurological changes in relation to that of monolinguals and on bilingual implications to dementia and ageing. Due to significant heterogenicity in the data a meta-analysis could not be performed.

Results and conclusions: Following analysis of the included papers, this review finds that bilingualism induces significant grey and white matter cerebral changes, particularly in the frontal lobes, ACC, left IPL and subcortical areas and that first and second languages largely recruit the same neuroanatomical structures but that these experience subtle functional and anatomical differences dependent on level proficiency and age of acquisition. There is adequate evidence to suggest that bilingualism offsets the symptoms and diagnosis of dementia and that

it is protective against both pathological and age-related cognitive decline. Bilingualism is also evidenced to significantly alter neuroplasticity and synaptogenesis. Whilst many of these neurological changes are known, more remains to be elucidated and the relationship between bilingualism and other neurological pathologies remains unclear.

Association of biofluid metabolites with Alzheimer's disease – a systematic review and meta-analysis

Unique Code: TP001021

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Topic: Ageing and dementia

Background

Alzheimer's disease is a debilitating and often devastating neurodegenerative disease. In recent years there has been a focus on identifying biomarkers for disease status and progression, which could be used to identify at-risk individuals and potentially assist in the development of preventative treatments. A systematic review was completed in order to synthesise such studies and identify biomarkers commonly identified as being modified in Alzheimer's disease.

Methods

Three databases (Embase, MEDLINE, and PsychInfo) were searched in order to identify suitable studies, 2010-2017. Results were screened and studies were excluded if the population or outcomes were unsuitable for the review. Meta-analyses were conducted using R version 3.3.3 for biomarkers that were investigated in the same biofluid, amongst studies with a sufficient amount of detail to allow meta-analysis.

Results

Out of 1725 identified results, thirty-seven studies were ultimately included in the systematic review. The study identified 702 unique extractable metabolite reports across the studies. We found metabolite changes indicating changes in choline, ceramide and monoamine metabolism. A further eight studies were suitable for inclusion in meta-analyses, covering 5 metabolites in 3 biofluids.

Conclusions:

A large number of biofluid metabolites have been identified that are altered in Alzheimer's Disease. However, studies investigating this area are highly heterogeneous in terms of methodologies and reporting standards, making meta-analyses difficult. In future, increasing numbers of studies with similar modalities may help provide clarity and more data regarding metabolites that are strongly linked to disease status.

Loss of consciousness in National Football League players is associated with high strain in the thalamus and brainstem

Unique Code:TP001022

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Topic: Ageing and dementia

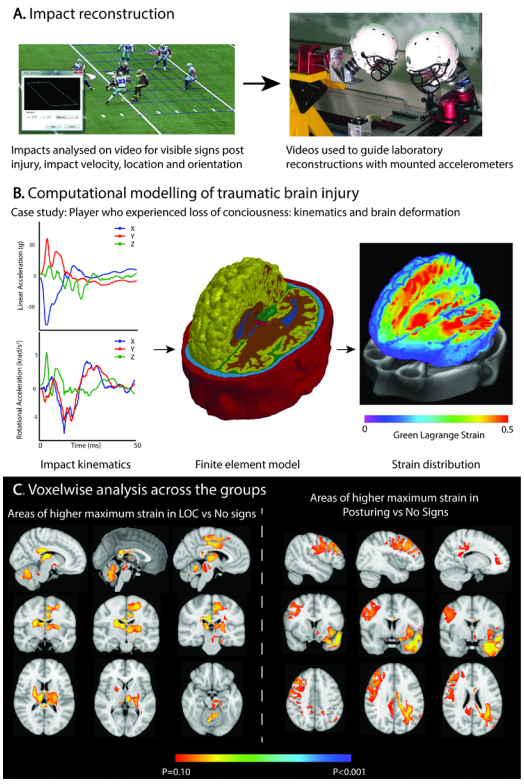
Sports traumatic brain injury (TBI) can produce transient neurological signs such as loss of consciousness (LOC) and dystonic posturing. However, it is unknown why impacts produce a range of neurological effects. Video surveillance allows the biomechanics of impacts to be calculated from impact reconstructions. The biomechanics can then be used to estimate the patterns of strain produced in different brain regions. Here we use a 3D model of brain injury biomechanics to investigate the strains produced by National Football League impacts that produce mild TBI leading either to LOC,

dystonic posturing, or producing no neurological signs. We test the hypotheses that LOC is associated with high strain within the brainstem and thalamus, whereas dystonic posturing is association with high strain in the motor cortex and/or corticospinal tracts.

82 videos of mild TBIs in the NFL were classified as showing either LOC (20), posturing (21) or no neurological signs (No Signs - 41). Methods are highlighted in Fig A & B. A one-way ANOVA was used to compare impact kinematics between the outcome groups of NFL players. A voxelwise analysis using the general linear model with non-parametric permutation testing (10,000) in FSL Randomise with and without 90th percentile strain as a covariate was used to compare strain data.

Impacts leading to LOC had significantly higher impact kinematics and whole brain measures of brain deformation compared to No Signs impacts. A voxelwise analysis of brain deformation corrected for the magnitude of strain showed regions of disproportionately higher strain in the thalamus, brain stem and cerebellum in impacts leading to LOC compared to No Signs (Fig C). Impacts leading to posturing also showed regions of higher strain, however these areas were constrained to the cortical regions including the motor cortex.

We show that strains are particularly high in the thalamus and brain stem in those players who lose consciousness. In contrast, impacts leading to posturing appear to disproportionately affect cortical regions, including the motor cortex. These results provide evidence that loss of consciousness is produced by head impacts that produce high strain in the brainstem and thalamus.



Preclinical modelling in the mouse of altered neuroinflammation in Alzheimer's disease – Down syndrome

Unique Code: TP001028

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Topic: Ageing and dementia

Introduction: People with Down syndrome (DS) develop Alzheimer's disease (AD) pathology, amyloid plaques and neurofibrillary tangles, by age 40 and the majority will develop dementia, due to having three copies of the chromosome 21 (Hsa21) gene APP leading to raised Aβ. How trisomy of the other Hsa21 protein-encoding genes affects AD is unclear. Neuroinflammation, an important aspect of AD, is changed in people with DS, and people with DS have general perturbations to their immune system, including elevated pro-inflammatory cytokine levels and an activated interferon response. Several genes on Hsa21 have been implicated in inflammation differences in DS, but how these genes when in three copies modify neuroinflammation in AD-DS is unknown. We are investigating how an extra copy of five Hsa21 candidate genes (RUNX1, IFNAR1, IFNAR2, IFNGR2, and IL10RB) modify neuroinflammation in response to Aβ.

Models: mice with three copies of Hsa21 orthologous genes in the mouse, including our five candidate genes; the Dp2Tyb strain (three copies of ~36 genes) and Dp1Tyb strain (three copies of ~148 genes).

Methods: real-time PCR, immunohistochemistry, MSD immunoassay. Univariate ANOVA used to assess effect of the factors genotype and sex on outcome measures.

Results: Having three copies of our candidate genes in the Dp1Tyb and Dp2Tyb models increases their expression in the brain. The Dp1Tyb model has elevated microglial number in the dentate gyrus of the hippocampus and elevated levels of several pro-inflammatory cytokines. The Dp2Tyb model has no changes to microglia number in the hippocampus but has elevated levels of interferon-γ in the cortex.

Conclusions: Interferon-γ is an activator of microglia, and people with DS have hyper-sensitivity to interferons due to three copies of our Hsa21 candidate genes IFNAR1, IFNAR2, IFNGR2, and IL10RB. Thus, the Dp2Tyb strain has elevated interferon-γ and raised IFN receptors levels that may modify the microglial response to Aβ. Next, to test this we will cross the Dp2Tyb strain with the NL-G-F model of amyloid pathology.

Complete microglia deficiency accelerates prion disease without enhancing CNS prion accumulation

Unique Code: TP001033

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Topic: Ageing and dementia

Introduction

Prion diseases are transmissible, neurodegenerative disorders to which there are no cures. Previous studies show that treatments that lead to the depletion of microglia accelerate prion disease and increases the accumulation of prions in the brain, suggesting that microglia provide neuroprotection by phagocytosing and destroying prions. In Csf1rΔFIRE mice, the deletion of an enhancer within the colony stimulating factor 1 receptor (Csf1r) gene specifically blocks microglia development, however, their brains develop normally with none of the deficits reported in other microglia-deficient models.

Methods

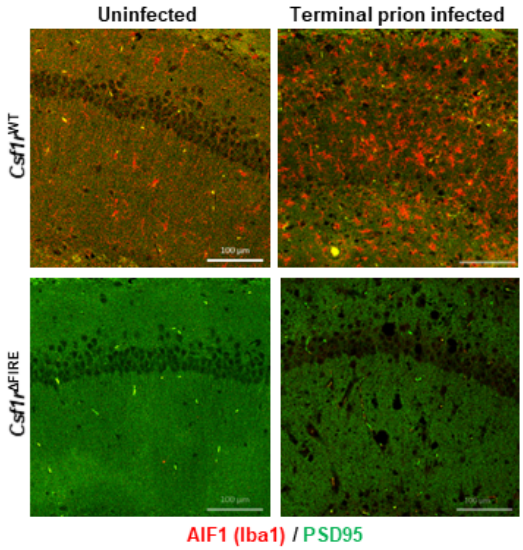
Csf1rΔFIRE mice were used as a refined model to study the impact of complete microglia-deficiency on central nervous system prion disease. Mice were challenged intracerebrally with ME7 mouse adapted scrapie prions and monitored for progression of prion disease by weekly clinical assessment and CatWalk automated gait analysis. Mice were sacrificed at defined humane clinical endpoints (terminal) and a group sacrificed at 98 days post infection to monitor rate of prion neuropathogenesis. Brains were assessed by neuropathological analysis including immunohistochemistry, Western blot, real-time quaking induced conversion (RT-QuIC), and reverse transcriptase quantitative polymerase chain reaction (RT-qPCR).

Approach for statistical analysis

Mice were grouped according to confirmed genotype and prion-challenge status. Survival curve analysis performed by Log-rank [Mantel Cox] Test. Image and gene expression analyses performed by Student's t-test or ANOVA. CatWalkXT analysis performed using two-way ANOVA. Values of $P < 0.05$ were accepted as significant.

Results

Csf1rΔFIRE mice succumbed to prion disease much earlier than wild-type mice as determined by both clinical assessment and gait analyses. This was not due to increased accumulation of prions in their brains. Instead, astrocytes displayed earlier, non-polarized reactive activation with enhanced synaptic pruning and unfolded protein responses. In conclusion, our data indicate that the microglia are not required for prion disease and provide neuroprotection independently of prion clearance by inhibiting neurotoxic reactive astrocyte activation.



Investigating Abeta-induced toxicity in tau-deficient human neurons

Unique Code: TP001038
Authors: Bryan Ng - Physiology, Anatomy and Genetics University of Oxford,
Topic: Ageing and dementia

Amyloid-beta (Ab) and tau aggregates are two major pathological hallmarks known to be dysregulated in Alzheimer's disease (AD), leading to widespread pathology. We now know from tau-deficient rodent models that tau does not merely facilitate Ab-induced toxicity but is also essential in that particular toxic cascade. Having an experimental model based on the human genetic and biological background is necessary to understand AD which does not happen naturally to rodent models. However, there is currently no tau-deficient human in vitro model available to corroborate these studies.

Here we generated the first isogenic human induced pluripotent stem cell (iPSC) lines lacking MAPT expression, which encodes for the tau protein, to study the effects of tau deficiency in human cells. We also established a versatile and scalable cortical neuron differentiation protocol by combining dual-SMAD inhibition and inducible Ngn2 expression, successfully producing a heterogeneous population of functional neurons manifesting cortical identity in co-culture with rat astrocytes. To further mimic the pathological environment, we extracted brain homogenate from a patient with AD to serve as the source of extrinsic Ab in addition to using synthetic Ab oligomers.

Here we have two isogenic panels of MAPT-/- lines. I conducted the statistical analyses only within the same isogenic panel. One-way ANOVA was used for baseline comparisons and two-way ANOVA was used for multiple treatment conditions.

iPSC-derived MAPT-/- cortical neurons showed lower functional activities than MAPT+/+ neurons by producing less action potentials, while expressing similar number of synapses. The MAPT-/- cortical neurons also demonstrated impaired axonal outgrowth over 5 days of live imaging. Upon the extrinsic AD brain homogenate and/or Ab1-42 oligomer insults, the MAPT-/- neurons appeared to be protected from axonal degeneration, cytotoxicity and functional hyperactivation as compared to the MAPT+/+ neurons. However, the Ab-induced synapse loss was still observed in the MAPT-/- background. Taken together, the absence of tau protein in human iPSC-derived cortical neurons results in various phenotypic impairments and can lead to neuroprotection in MAPT-/- neurons from Ab-induced toxicity.

Differential chemokine changes are seen in the different variants of primary progressive aphasia

Unique Code: TP001046
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Topic: Ageing and dementia

Introduction:
The primary progressive aphasias (PPA) are degenerative disorders presenting with language impairment. Each variant of PPA is characteristically associated with a different pathological form: nonfluent variant (nfvPPA) and semantic variant

(svPPA) with frontotemporal lobar degeneration (FTLD) pathologies and logopenic variant (lvPPA) with Alzheimer's disease (AD) pathology. Previous studies have suggested a role for inflammation in these disorders, and so we aimed to investigate the concentrations of a panel of chemokines in cerebrospinal fluid (CSF) and plasma samples from individuals with PPA as well as healthy controls.

Methods:
A total of 55 participants were recruited to the study: 11 with svPPA, 13 with nfvPPA, 12 with lvPPA and 19 age-matched controls. CSF and plasma samples from all participants were assessed using the Olink® Proximity Extension Assay inflammatory panel which measures the concentrations of 20 chemokines: CCL2 (MCP-1), CCL3 (MIP-1a), CCL4, CCL7 (MCP-3), CCL8 (MCP-2), CCL11, CCL13 (MCP-4), CCL19, CCL20, CCL23, CCL25, CCL28, CX3CL1, CXCL1, CXCL5, CXCL6, CXCL8 (IL-8), CXCL9, CXCL10, and CXCL11.

Approach for statistical analysis:
D'Agostino & Pearson omnibus normality test was performed to determine the normality of distribution. Unpaired t-test with Welsh's correction or non-parametric Mann-Whitney U test was done for compare each group.

Results and conclusions:
In the CSF, CCL3 and CX3CL1 concentrations were increased in lvPPA (mean 2.76 (standard deviation 0.42), p = 0.0497; 3.82(0.41), p=0.0216 respectively) compared with controls (2.46(0.32); 3.45(0.39)). In contrast, CCL19 and CXCL5 concentrations were decreased in both svPPA (7.13(1.52), p=0.0242; 2.88(0.44), p=0.0163) and nfvPPA (7.62(1.1), p=0.0493; 2.76(0.83), p=0.0408) compared with controls (8.44(1.11); 3.32(0.46)). Finally, CXCL6 showed a decrease only in svPPA (2.48(0.74)) when compared with the controls (3.07(0.69), p=0.0449. Few changes were seen in plasma.

These results show abnormal chemokine concentrations in the CSF of people with PPA, and differential involvement of chemokines between lvPPA (an atypical form of AD) and both svPPA and nfvPPA (both non-Alzheimer, FTLD disorders), revealing the complexity of the inflammatory response in PPA.

Novel pathway enrichment and network analysis methods for investigating selective vulnerability to pathological tau in Alzheimer's Disease

Unique Code: TP001056
Authors: Emir Turkes - UK Dementia Research Institute University College London, Karen E. Duff - UK Dementia Research Institute University College London,
Topic: Ageing and dementia

Background: Region-specific neuronal subpopulations known to be selectively vulnerable and resistant to tau pathology, as characterized in our previous work (Fu et al., 2019), were identified across several public single-cell/nucleus RNA seq datasets and analysed using novel bioinformatic methods to better understand the factors underlying selective vulnerability.

Methods: In this poster, we show an analysis conducted using wild-type mouse SMART-Seq data from the Allen Brain Institute (Hodge et al. 2019). Following a standard preprocessing and exploratory analysis pipeline, we applied a custom differential pathway enrichment and network analysis pipeline that identifies features that co-vary with the vulnerability

status of a cell-type.

Results: We show that using known marker genes, we were able to identify highly specific clusters of cells that correspond to cell-types that exhibit selective vulnerability. Our novel pathway/network analysis pipeline demonstrates that through trajectory inference, we can identify putative pathways and genes that underlie selective vulnerability.

Conclusion: We present a novel pathway enrichment and network analysis pipeline and demonstrate its application in single cell RNA seq data for uncovering pathways and genes that are associated with selective vulnerability in Alzheimer's Disease.

Delivery of cobalt complexes to the brain with focused ultrasound to treat Alzheimer's disease

Unique Code: TP001061
Authors: Sophie Morse - Bioengineering Imperial College London,
Topic: Ageing and dementia

Focused ultrasound and microbubbles can be used to non-invasively, locally and transiently open the blood-brain barrier (BBB), allowing drugs into the brain. Recently, a series of cobalt complexes have been designed and shown to prevent the aggregation of amyloid-beta (Aβ) in vitro, which is characteristic of Alzheimer's disease. However, these complexes are not able to cross the BBB. Here, we investigated whether ultrasound could deliver these cobalt complexes into the brain in vivo and evaluated whether a therapeutic effect could be obtained in an Alzheimer's disease mouse model.

We first investigated the toxicity of delivering the cobalt complexes across the BBB using ultrasound in wild-type C57BL/6J mice (weekly for four weeks). A preliminary efficacy study was then carried out in a 5xFAD Alzheimer's mice to determine any effects of the complexes on the Aβ burden in the brain following three weekly treatments. Mice were treated with ultrasound emitted in a rapid-short-pulse sequence onto the left hippocampus, which we have designed to produce a safe and efficient delivery. The cobalt complex and SonoVue microbubbles were administered intravenously during the ultrasound treatment. The mice were split into 5 treatment groups (no treatment, vehicle only, cobalt complex only, ultrasound only and ultrasound + cobalt complex). Thioflavin-S and MOAB-2 staining were performed on the brain slices to assess changes in the overall Aβ burden and the amount of Aβ fibrils, whose formation is inhibited by these complexes. Unpaired Student t-tests were performed between treatment groups ($P < 0.05$).

The cobalt complex was successfully delivered to the brain with focused ultrasound. Its delivery was well-tolerated given that no changes in body weight or tissue morphology were observed in the wild-type mice following four weekly treatments. Our preliminary data in transgenic 5xFAD mice suggests that the cobalt complexes are exerting a therapeutic effect with a reduction in Aβ burden observed between no treatment controls and the mice treated with ultrasound and the complex. These results indicate a promising therapeutic strategy using a safe and efficient ultrasound delivery method.

Dementia Inpatients With and Without COVID-19: Clinical Needs, Care and Outcomes

Unique Code: TP001066

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Topic: Ageing and dementia

Background:
Dementia is the most common pre-existing condition related to coronavirus deaths. COVID-19 itself causes high rates of neuropsychiatric co-morbidities, including delirium. In addition, infection control measures in hospitals and changes in patient flow have drastically altered the care provided to patients with dementia. Some of the emergency measures mainly affected COVID-19 positive patients, whereas others had an impact on all. The difference in dementia care and health outcomes between patients with and without coronavirus is not well characterised.

Methods:
This project examined these differences by leveraging the National Audit of Dementia (NAD) data framework. A tailor-made questionnaire was composed of the relevant items from the NAD and additional items - demographic data, details of care provided, health and discharge outcomes. The sample included 100 patients with dementia admitted to the Stoke Mandeville Hospital during April-July 2020. This was composed of all dementia patients who tested positive for COVID-19 during admission (n=25) and a control sample of those who did not (n=75).

Statistical analysis:
Analysis involved a combination of student's t, binomial, and Chi-squared statistical tests, applied to numerical, two-answer categorical, and multiple-answer categorical data respectively. Where appropriate, false discovery rate correction was applied to account for multiple comparisons. P-values of <0.05 were treated as representing significant differences between the groups.

Results and Conclusions:
Demographics of COVID-positive dementia inpatients were different, with more males (48% vs. 27% of COVID-negative) and more patients coming from residential care (40% vs. 19%). During admission, COVID-positive patients experienced higher rates of new neurological signs and delirium, but fewer formal assessments of cognition were carried out. On the other hand, COVID-positive inpatients received better functional assessments and comprehensively documented ward-care. While the mortality rate for these patients was much higher (48% vs. 8%), if discharged, this was better coordinated. Distinct clinical needs of COVID-19 dementia inpatients need to be taken into account in the planning of routine, and crisis, hospital care.

Early-stage hippocampal hyperexcitability and impaired synaptic plasticity in the TgF344-AD rat model of Alzheimer's disease

Unique Code: TP001091

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Neuroscience@Nottingham The University of Nottingham, Dr John Gigg - Division of Neuroscience & Experimental Psychology The University of Manchester, Dr Michael Harte - Division of Pharmacy & Optometry The University of Manchester ,
Topic: Ageing and dementia

Introduction
Hippocampal hyperexcitability has been implicated in cognitive deficits at early stages of Alzheimer's disease (before Aß plaque formation). Here, we investigated if early changes in behaviour and hippocampal excitability can also be observed in the TgF344-AD transgenic rat model of Alzheimer's, which expresses APPsw and PS1ΔE9 genes.

Methods
At the age of 3, 6 and 9 months, male and female TgF344-AD rats and wild-type (F344) littermates (n=6-13/sex-genotype combination) were tested for: (i) hippocampus-dependent rapid place learning in a delayed-matching-to place watermaze (DMP) test, (ii) novel object recognition (NOR), (iii) expression of startle/pre-pulse inhibition; and (iv) open-field locomotor activity. In further cohorts (n=8) of 9 month-old male TgF344-AD and control rats, evoked field excitatory post-synaptic potentials (fEPSPs) were recorded in vivo under urethane anaesthesia to compare baseline synaptic connectivity as well as short- and long-term synaptic plasticity (STP/LTP) in the Schaffer collateral pathway (CA3-->CA1).

Statistical analysis
Data were analysed using multi-factorial ANOVA, including sex and genotype as between-subjects and age as repeated-measures factor.

Results
Behaviour: F344 rats showed poor DMP performance with no clear genotype effect. Object exploration was low with no significant NOR. We found startle and locomotor sex differences, replicating previous reports. Interestingly, at 9 months, Tg344-AD rats showed locomotor hypoactivity at the beginning and hyperactivity at the end of the 30-min open-field test, indicating impaired habituation, which may reflect impaired hippocampal contextual memory.

Electrophysiology: 9 month-old TgF344-AD rats showed reduced LTP and STP. They also showed larger baseline CA1 fEPSPs and increased CA3-CA1 connectivity, which may partly account for reduced synaptic plasticity in the TgF344-AD rats.

Conclusions
Poor memory performance limits the suitability of TgF344-AD rats for testing clinically relevant memory deficits, although impaired locomotor habituation suggests aberrant hippocampal function emerges around 9 months. This is supported by our electrophysiological findings of marked synaptic hyper-excitability with impaired plasticity in CA1 at this age.

Investigating microglial lysosome function and the role of cystatin F in inflammation and neurodegenerative disease

Unique Code: TP001104

Authors: Mike Daniels - UK Dementia Research Institute, Centre for Discovery Brain Sciences UK Dementia Research Institute at The University of Edinburgh

Topic: Ageing and dementia

Introduction

Inflammation is proposed to play a key role in neurodegeneration. Microglia, the major resident immune cells of the CNS parenchyma, become activated in many disease paradigms. Recent studies have demonstrated that a particular type of activated microglia emerge in several models of neurodegenerative disease. We currently do not understand exactly how these disease-induced microglia affect neurodegeneration. Among the most highly enriched gene sets in the disease-induced cluster are lysosomal genes, in particular Cst7 (encoding cystatin F (CF)), a lysosomal protease inhibitor. Here we aim to investigate what effect CF has on microglial function in the context of inflammation and neurodegeneration.

Methods

Specific probes Gly-Phe-AMC (Cathepsin C) or Z-Phe-Arg-AMC (Cathepsin L) were used to measure cathepsin activity in bone marrow-derived macrophages (BMDMs) or primary microglia from WT or Cst7-/- mice. pHrodo-tagged S.aureus bioparticles or human synaptoneurosomes were used to investigate phagocytosis. HiLyte-647-tagged Aβ was used to investigate Aβ degradation. LPS and IL-4 were used to investigate the response of BMDMs or primary microglia to immune stimuli by qPCR and ELISA.

Approach for statistical analysis

Cathepsin activity data were analysed by t-test whilst qPCR and ELISA data were analysed by 2-way ANOVA to assess gene effect or treatment effect. Phagocytosis and degradation date were analysed first by calculating area under curve then by 2-way ANOVA.

Results and Conclusions

CF-deficiency led to basal increase in cathepsin activity in BMDMs but not primary microglia. Phagocytosis of S.aureus bioparticles or human synaptoneurosomes by Cst7-/- BMDMs or primary adult microglia does not differ from WT, suggesting CF does not regulate phagocytosis directly. Additionally, CF deficiency does not affect ability of BMDMs to degrade aggregated Aβ, a process dependent on cathepsins. Finally, we showed that CF deficiency does not affect response of BMDM or primary adult microglia to broad immune stimuli. In conclusion, we have shown that Cst7 deficiency does not affect microglial function in vitro suggesting CF is not involved regulating microglial function under homeostasis.

Dysfunctional nucleocytoplasmic transport dynamics in amyotrophic lateral sclerosis and frontotemporal dementia caused by mutation in C9orf72

Unique Code: TP001106

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Topic: Ageing and dementia

A mutation in the C9orf72 gene is the most common genetic cause of the devastating neurodegenerative diseases amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). To date, no effective treatments for these disorders exist. The C9orf72 mutation results in the production of neurotoxic dipeptide repeat proteins (DPRs). Modifier and interactome studies suggest that DPRs affect nucleocytoplasmic transport. Altered nucleocytoplasmic transport is likely to contribute to disease pathology as this vital mechanism is the main route of information exchange between the cell's cytoplasmic and nuclear compartments.

Smaller molecules can passively diffuse through the nuclear pore, the protein complex through which transport occurs. Conversely, larger molecules need to be actively transported by receptors. We have optimised an assay to specifically investigate passive nucleocytoplasmic transport monitoring inert fluorescent cargo of different sizes using live confocal microscopy which is analysed using linear and non-linear regression methods. Studying passive diffusion in a disease context yields information about nuclear pore integrity and function. In addition, passive diffusion is thought to be the main route of nuclear export of key ALS/FTD proteins TDP-43 and FUS.

We have found that arginine containing C9orf72 DPRs significantly alters passive transport of reporter as well as disease relevant cargo molecules in a size-dependent manner. Therefore, while the leakiness of the nuclear pore is altered, its permeability barrier is maintained in the presence of C9orf72 DPRs. We are now investigating potential mechanisms of action. Thus, this study will inform on interactions between the nuclear pore and C9orf72 DPRs and identify potential new therapeutic targets.

Affective and Cognitive deficits in a novel AD mouse model: A role for Noradrenaline and Inflammation

Unique Code:TP001117

Authors: Katie Sedgwick - Psychology Cardiff University

Topic: Ageing and dementia

Introduction

Depression has been robustly linked to Alzheimer's disease (AD) often occurring before the onset of cognitive decline. The affective symptoms that accompany this decline are also frequently overlooked but could offer insights into the early stages of the disease and how it progresses. To examine this link in detail, animal models are useful in offering a controlled platform to investigate whether affective deficits are merely a symptom or play a significant role in disease onset. Furthermore, gender is rarely considered despite being an important risk factor for AD, so understanding sex differences in disease progression will further aid this mechanistic research. Thus we have assessed affective and cognitive deficits in an AD mouse model which are considered alongside neurological insults of relevant brain areas (e.g. Locus Coeruleus (LC)) and inflammation.

Methods
The AppNL-G-F knock in mouse was used with behavioural analysis to examine affective and cognitive deficits in a young cohort (n=96) aged 5-7 months using Open field, Object in Place, Social preference test, elevated plus maze and Lick Cluster analysis. Immunohistochemistry stain for Tyrosine Hydroxylase will show any insults to the LC while a plaque and microglia stain will spatially show the inflammatory response around amyloid aggregation.

Approach for statistical analysis
Bayesian statistical methods were adopted to explore genotype and gender differences within behavioural testing and densitomotry analysis for the immunohistochemistry.

Results and Conclusions
At this early time point, no affective or cognitive deficits were found aside from a reduction in distance moved by the AppNL-G-F in the open field. This could be indicative of a depressive-like symptom but, in the absence of other deficits, appears not to be. There were no significant gender differences in any of the tests and the absence of behavioural effects are considered in relation to degree of neurological insult. As expected, the young cohort exhibited few deficits which, in the future, will be compared to an older cohort (12-14 months) to examine the progression of affective symptoms in relation to LC damage, inflammation and amyloid pathology.

Investigating antibody mediated neutralisation of tau in a new organotypic hippocampal slice culture model of seeded aggregation

Unique Code: TP001129
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Topic: Ageing and dementia

Introduction: Assemblies of the protein tau characterise multiple neurodegenerative diseases. There are currently multiple clinical trials targeting the protein tau for degradation using antibodies, however it is still unknown by what mechanism this can be achieved most effectively. We have previously shown that antibodies can protect against the seeded aggregation of tau in reporter cell lines via the intracellular Fc receptor TRIM21. We set out to investigate whether the same mechanism is at work in neural tissue. Due to the lack of control in vivo injection experiments provide, we developed a more accessible and tractable model in which to investigate the ability of antibodies to protect against tau pathology.

Methods: We prepared organotypic hippocampal slice cultures (OHSCs) from P301S transgenic mice and maintained them at a liquid-air interface for up to five weeks. Tau pathology was examined by immunofluorescence microscopy.

Approach for statistical analysis: Binary threshold-based masks were applied in ImageJ, and percentage AT8 reactivity

was determined in regions of 100 x 100 µm. Data was analysed via the Kruskal-Wallis test by ranks, unless it was determined to be normally distributed, in which case a one-way ANOVA was employed. All statistics were carried out in GraphPad Prism Version 8.

Results and Conclusions: Whilst untreated OHSCs displayed no overt signs of pathology, exposure to extracellular tau assemblies could result in the formation of intraneuronal, hyperphosphorylated tau structures. Interestingly, we found the seeding ability of tau assemblies did not titrate in a manner that would be expected of independently acting particles. Rather, we observed that seeded aggregation only occurred over an apparent threshold, measured at around 100 nM of supplied tau assemblies. We found that the anti-tau antibody BR134 was able to provide a near-complete protection against tau pathology in this model. We have previously shown that this antibody does not block entry of tau into cells; ongoing work is therefore aiming to determine if the tau assemblies are also being degraded by intracellular Fc receptor TRIM21, or whether other players such as microglia may be involved in this more complex system.

Defective dopamine release from iPSC-derived dopamine neurons harbouring Parkinson's disease-associated SNCA-triplication

Unique Code: TP001131

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Topic: Ageing and dementia

Introduction & Aims: Parkinson's disease (PD) is a disorder in which the degeneration of dopaminergic neurons (DAns) in the nigrostriatal pathway leads to debilitating motor symptoms. There remains to be a unifying hypothesis for how this degeneration is initiated and because of this, no disease-modifying therapeutics are available. Evidence from several animal models of familial PD indicates that defective dopamine release is an early cardinal feature of PD, preceding both neuron death and symptom onset [1, 2]. Therefore, we aimed to address whether dopamine release is dysfunctional in human dopamine neurons from PD-affected individuals and the molecular mechanisms by which this occurs.

Methods & Statistical approach: We produced induced pluripotent stem cell (iPSC)-derived dopamine neurons from patients with PD-associated mutation SNCA-triplication using a modified Krik's protocol [3]. KCl-evoked dopamine release and total intracellular dopamine content were measured using high performance liquid chromatography electrochemical detection (HPLC-ECD). Data was normalized to protein concentration and compared using a Student's t-test.

Results & Conclusions: We observed a ninety percent decrease in release from iPSC-DAns harbouring SNCA-triplication and found that this coincides with a decrease in total intracellular dopamine content of the same magnitude. Both defective release and content were restored by acute L-DOPA treatment. We suggest these defects are not due to defective dopamine synthesis, but rather alterations in its handling. Combined, these data provide support from human models that synaptic dysfunction occurs early in PD. Results from this study will be critical to providing novel targets for the development of effective disease-modifying therapeutics.

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Identifying the neural and behavioral correlates of cognitive reserve

Unique Code: TP001133

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Topic: Ageing and dementia

Objective: In dementia, there is not always a one-to-one relation between the severity of the neuropathology and the degree of cognitive decline. This may be explained by a compensatory mechanism of cognitive reserve. The current study examined whether behavioral and neural correlates of cognitive reserve can be found.

Methods: 38 elderly healthy participants carried out a sustained attention task under two levels of arousal: alert and drowsy. Here, cognitive reserve was operationalized as the degree to which task performance was affected under drowsiness compared to alertness. We then related our measure of cognitive reserve with IQ, educational level, cognitive performance, structural volumetric differences in hippocampal subfields, and informational complexity as established by the Lempel-Ziv (LZ) algorithm.

Results: LZ increased under drowsiness, and a higher difference in LZ between alertness and drowsiness correlated with better performance under the neurocognitive strain of drowsiness. Furthermore, higher volume in various hippocampal subfields, such as CA1 and CA3, was related to higher cognitive reserve as indicated by a negative correlation between volume and performance discrepancy. However, IQ, educational level or other psychological measures failed to show any consistent relationship with cognitive reserve.

Conclusion: The findings of our study suggest a relationship between an increase of informational complexity under neurocognitive strain and task performance. This may reflect a compensatory mechanism, where individuals that have a more pronounced increase are better able to maintain their performance under neurocognitive strain. Furthermore, it might be that certain hippocampal subfields are involved in maintaining performance under neurocognitive strain. However, it is important to further investigate the functions of the various hippocampal subfields, their connectivity with other brain regions, and examine whether volumetric differences in other key regions for cognition may also be associated with cognitive reserve.

Tau accelerates an ageing phenotype that disrupts population activity in the visual cortex of mice

Unique Code: TP001147

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Topic: Ageing and dementia

Introduction: Neurofibrillary tangles composed of hyperphosphorylated tau are hallmarks of tauopathies, such as Alzheimer's Disease. The progression of tau deposits correlates with cognitive decline but the effects on cortical function are still unclear. In vivo imaging in mice reveals hypoactivity and neuron silencing when assessing spontaneous activity (Marinković et al., 2019, Busche et al., 2019). Here we investigate the effects of tau seeding on stimulus-driven activity in mouse primary visual cortex (V1).

Methods: We compared wild-type and P301S mice (model expressing human tau harbouring the P301S mutation associated with frontotemporal dementia). At 8-10 weeks, V1 was injected with a virus driving expression of the fluorescent Ca2+ sensor GCaMP6f and synthetic preformed fibrils (K18). Pyramidal cell (PC) activity in layer 2/3 was imaged by multiphoton microscopy in awake mice on a trackball and stimuli delivered as drifting gratings (80% contrast, 20□, 1 Hz, 0.04 cpd).

Statistical approach: We used linear regression line comparison and ANOVA tests.

Results and conclusions: We find that seeding with K18 accelerates changes in the functional organisation of V1 that also appear with age; a decrease in the proportion of PCs that are visually responsive, and an increase in the unresponsive proportion. Within the population of PCs that remain visually-driven, K18 injection also reduced the average amplitude of calcium responses and the degree to which activity was synchronised across the population – a property shown to depend on the number of excitatory inputs each neuron receives (Okun et al., 2015). The proportion of stimulus suppressed PCs also increased with age. K18 injection did not affect the size of this population, consistent with tau exerting weaker effects on inhibitory inputs. In cortical circuits, neurons process information as populations. These results indicate that local tau accumulation fundamentally disrupts this property by causing some PCs to "drop-out" of normal activity, with the remainder becoming less synchronised. Both these changes in V1 function might be explained by a loss of the normal excitatory inputs to this region. It will be interesting to understand how far tau affects population activity in other regions of cortex.

Uncovering human brain DNA methylation landscapes in frontotemporal lobar degeneration

Unique Code: TP001162

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Topic: Ageing and dementia

Introduction: Frontotemporal lobar degeneration (FTLD) is a term used to describe the neuropathology of frontotemporal dementia, the second most common form of early onset dementia. The current neuropathological classification of FTLDs recognises five major subgroups, three of which are characterised by specific proteinaceous inclusions: transactive response DNA-binding protein (TDP-43) in FTLD-TDP, tau in FTLD-TAU, and fused in sarcoma (FUS) in FTLD-FUS. Although DNA methylation changes have been consistently associated with neurodegenerative diseases, including Alzheimer's disease, little is known in FTLD. The main goal of this study was to explore DNA methylation signatures associated with FTLD-TDP, and overlay these signatures with downstream changes in protein levels. Methods: We dissected post-mortem frontal cortex grey matter tissue of pathologically confirmed FTLD cases and heathy controls. We profiled genome-wide DNA methylation patterns in these brain samples using the Illumina EPIC arrays, which covers over 850,000 methylation sites. Approach for statistical analysis: We performed differential methylation analysis using

regression models, and weighted gene correlation network analysis to identify co-methylation signatures. We compared these signatures with available proteomics data from FTLD-TDP cases and controls. Results and conclusions: We found a DNA methylation signature inversely correlated with the disease age at onset (r=-0.7, p=3x10-4), and nominally correlated with the FTLD-TDP status (r=0.44, p=0.04). We also found a co-methylation signature inversely correlated with the disease duration (r=-0.67, p=7x10-4). These signatures contain genetic risk factors for FTLD (e.g. SORT1 and ATXN2), as well as genes encoding for proteins that are dysregulated in FTLD-TDP. Functional enrichment analysis of these signatures suggests that higher levels of methylation in genes involved in axon guidance and RNA metabolism pathways may lead to an earlier appearance of the disease, and that with increasing disease duration there is a decrease in DNA methylation levels at genes involved in infection and transcription related pathways. Our data supports a role for DNA methylation in the pathogenesis of FTLD-TDP.

Proteomic investigation of the Alzheimer's risk gene MEF2C in microglial like cells

Unique Code: TP001164

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Topic: Ageing and dementia

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder for which there are no disease-modifying therapies. Genome-wide association studies and next-generation sequencing have identified over 50 susceptibility loci for AD. These include loci containing the transcription factor MEF2C, a master regulator of microglia development and function. In microglia, AD risk single nucleotide polymorphisms (SNPs) are enriched in open chromatin regions that contain DNA binding motifs for MEF2C. Disrupted DNA binding due to genetic variation at these sites or altered gene expression in cis may lead to impaired transcriptional control by MEF2C. This implicates the MEF2C transcriptional network as genetic risk mechanism of AD and investigation into the MEF2C interactome in microglia may provide functional and mechanistic insights into the molecular processes involved in AD pathogenesis. To explore this, Co-IP-Mass Spectrometry of endogenous Mef2c has been used to identify its protein isoforms, post-translational modifications, upstream regulators and interacting partners which may be integral to its biological function. The first Co-IP-MS interactome of Mef2c in microglia-like cells will be presented. Protein partners of this AD-relevant transcription factor have been identified after rigorous filtering against a negative control. SAINTexpress was used to statistically analyse the putative interacting proteins. These proteins include a novel interactor Oasl1 which is involved in the innate immune response, the transcriptional repressors Hdac4 and Hdac5, and members of the Hira complex which appear to be holding Mef2c predominantly in a repressed state in basal BV2 cells. The identification of these partners allows for a better understanding of Mef2c regulation and function as a master regulator of microglia and AD risk. This has provided insights into the molecular processes involved in AD, and the pathways through which AD relevant biology is regulated.ant biology is regulated.

Tubulin and its post-translational modifications in vascular dementia and Alzheimer’s disease

Unique Code: TP001180

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Topic: Ageing and dementia

Alzheimer's disease (AD) and vascular dementia (VaD) are the two most common forms of dementia in older people. Although they differ in their aetiology, they share pathophysiological features, such as neuronal loss and loss of tau protein in the temporal lobe. Neuronal and synaptic loss are the best predictors for cognitive decline. In apoptosis, the cytoskeleton undergoes significant morphological changes due to the disruption of microtubules (MTs), the main protein of the cytoskeleton. MTs take part in a variety of functions, such as cell motility, shape, polarity, transport or mitosis. They are also essential for synaptic plasticity and their integrity and stability is crucial for proper neuronal functioning. Stabilization of MTs is achieved either through interactions with MT binding proteins (MTBPs) or by posttranslational modifications (PTMs) of tubulin. Some of these PTMs regulate the binding between MTs and MTBPs, and thus, may play a role in neurodegeneration. We hypothesize that tubulin might undergo various PTMs, which precede the observed tau and neuronal loss. 37 samples of human brain homogenates - Controls (C; n = 13), VaD (n = 13) and AD (n = 11) – were analysed by Western Blot (WB). The levels of alpha1 and beta3 tubulin (the most abundant tubulin isotypes in the brain) were measured, as well as the following PTMs: polyglutamylation (PolyE), tyrosination (Tyr), detyrosination (DeTyr), delta2 tubulin and acetylation. For the statistical analysis, One Way-ANOVA test was used, followed by a Tukey's multiple comparison test. We found that alpha1 tubulin is significantly increased in VaD, whereas beta3 tubulin is significantly decreased in AD. In addition, there was a non-significant decrease of acetylated tubulin, as well as a significant decrease in DeTyr tubulin in VaD when compared to C, whereas both types of dementia showed a non-significant increase in PolyE.

The effect of memantine on cortical network function in frontotemporal lobar degeneration is conditional on baseline GABA physiology

Unique Code: TP001186

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Topic: Ageing and dementia

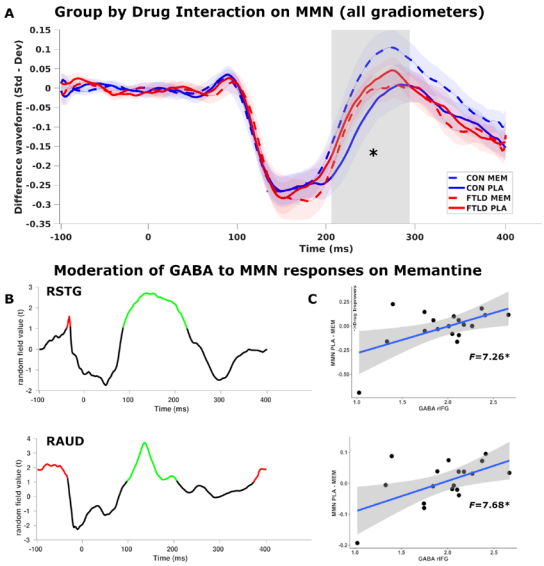
Frontotemporal lobar degeneration (FTLD) is associated with deficits to GABA and glutamatergic neurotransmitters in the frontal cortex. While targeting GABAergic systems has shown to restore frontotemporal deficits in FTLD, little is known whether pharmacological probes of glutamate have similar effects in these circuits.

Twenty participants with a FTLD-associated syndrome and 20 healthy-controls undertook two magnetoencephalography (MEG) sessions during a roving auditory oddball task assessing frontotemporal change detection: (1) session on placebo and (2) 10mg of oral memantine, which aims to blocks glutamatergic excitotoxicity. The mean amplitude of MEG "mismatch negativity" responses (MMN; standard-deviants, 125-175ms) were calculated across gradiometer sensors and for bilateral frontotemporal sources. Glutamate and GABA levels were measured using 7T proton magnetic resonance spectroscopy of the right inferior frontal gyrus (IFG).

Frequentist and Bayesian ANOVAs assessed the differential mean MMN responses between controls and patients across placebo and drug conditions. Evoked difference waveforms (standard-deviants) across the peristimulus time-window were analysed using random field theory (RFT) (crit p=0.05, FWER) for the effects of interest.

Patients and controls did not demonstrate differential mean MMN amplitudes on placebo at the average-sensor (p=0.95) or source-level (p>0.27) (BF10=0.3-0.5). Across sensors, only controls exhibited a differential drug-dependent MMN, reflected by a steeper rebound of difference waveforms between 206-288ms on memantine (Fig 1A; pFWER=0.026, cluster-level). However, no interaction was found for mean MMNs (p>0.053). Notably, RFT (Fig 1B) and linear mixed models (Fig 1C) identified greater GABA levels in patients are significantly associated with stronger MMN responses in right-hemisphere areas under memantine. Glutamate levels did not moderate the mean MMN response to memantine (p>0.065).

We show targeting glutamatergic systems does not lead to a restoration of frontotemporal physiology across patients. However, the effects of memantine are conditional on patient's baseline GABA, suggesting a critical balance between glutamatergic and GABA physiology that may underlie the large-scale neural deficits in FTLD.



A) Mean evoked difference responses for controls (CON) and FTLD patients on placebo (PLA) and memantine (MEM): *, group by drug interaction ($p<0.05$, FWER, cluster-level). B) t-stats at each peri-stimulus time point for drug by GABA interaction in the right superior temporal gyrus (RSTG) and auditory cortex (RAUD): Clusters of t-values ($t>1$) surviving FWER-correction are shown in green, red are those which do not. C) Association of GABA levels with differences in mean MMN amplitudes (125-175ms) across PLA and MEM. * $p < 0.05$, linear mixed models.

Chemogenetic activation of midline thalamic nuclei does not amerliorate behavioural deficits in hAPP-J20 mice or Tg4510 mice

Unique Code: TP001200

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Topic: Ageing and dementia

Introduction: Alzheimer's Disease (AD) is marked by the progressive loss of memory due to pathological changes within the Papez circuit. The subsequent degeneration can increase dysfunction of communication within local circuits and between brain regions. The thalamus is at the centre of this extended memory circuit, and we hypothesised that altering the intrinsic excitability of cells within thalamic nuclei by the use of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), may improve deficits seen in learning and memory in mouse models for dementia.

Methods: Ninety-six male and female hAPP-J20 mice (WT n=49, HET n=47) and thirty-eight male Tg4510 mice (WT=18, TG n=20) received a unilateral intracerebral injection into the nucleus reuniens (NRe) or bilateral injection into the anterio-dorsal/anterio-ventral (ATN) nuclei of either AAV8-hSyn-hM3Dq(Gq)-mCherry or AAV8-hSyn-mCherry as a control. At nine and six months of age respectively, mice underwent a behaviour battery of open field (OF), novel object recognition (NOR) and radial arm maze (RAM). For the latter, mice were restricted to 90% bodyweight prior to test start, with 50% condensed milk used as a food reward. 1mg/kg Compound agonist 21 was administered subcutaneously 30min prior to each behaviour test. Tissue was collected post-behaviour to confirm injection site and virus expression.

Results: Both Tg4510 and hAPP-J20 mice show marked hyperactivity in the OF ($p<0.0001$), significant deficits in recognition memory ($p<0.0001$), and a significant impairment in spatial reference ($p<0.0001$ and $p=0.023$) and spatial working ($p<0.0001$ and $p=0.04$) memory, respectively, compared to controls. Increased neurotransmission efficiency in the NRe or ATN, by the use of Gq-coupled DREADDs however, did not significantly improve these memory impairments or reduce the observed hyperactivity.

Discussion: The approach used herein suggests that despite the important role of the thalamus in information processing, the specific sub-region activation of thalamic nuclei is not sufficient to ameliorate the behavioural deficits in these models. This may be due to compensation elsewhere within the memory circuit, or that the pathological changes are too far advanced for behaviour reversal.

Maintenance of endogenous ApoE in acute brain slices for electrophysiological recordings

Unique Code: TP001218
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Topic: Ageing and dementia

ApoE is a secreted protein that plays a central role in transporting lipids between cells in the brain. A genetic variant of ApoE, ApoE4, is implicated as the major risk factor in Alzheimer's Disease and yet it's effects on neuronal function are poorly understood. Some of the trouble in establishing the impact of ApoE on neurophysiology may arise from difficulties in maintaining secreted ApoE in tissue during ex vivo electrophysiology. We hypothesized that ApoE is poorly retained in brain slices when submersed in artificial cerebral spinal fluid (aCSF) during routine slice recovery and recording methods.

To test this, brain slices were prepared from 6m old WT mice in ice-cold sucrose-based cutting solution and recovered for 1 hour at room temperature in a standard aCSF submersion chamber. To exclude the possibility of enzymatic degredation of ApoE, cell-impermeant protease inhibitors were included in the aCSF. Some slices were also recovered at the aCSF:air interface on a dialysis membrane with a molecular weight cut-off below the size of ApoE to prevent ApoE diffusing out of the slice. Western blots were then prepared from slice extracts and probed for ApoE and beta-tubulin (control). Patch-clamp and field potential recordings were performed on multiple recovered slices to visualise the functional health of cells. The data was then fitted to a linear mixed effects model of the signal against recovery and slicing condition before post hoc sidak corrected pairwise comparisons were performed.

After 1-hour recovery at room temperature in a submersion chamber, total ApoE protein levels in slices decreased by ~50 % ($p < 0.0001$). In contrast, slice ApoE levels were unaffected when recovered instead on the dialysis membrane

interface. Punching holes in the dialysis membrane then restored the loss of ApoE ($p < 0.05$). Furthermore, brain slices remained healthy allowing extracellular field potential recordings and whole cell patch-clamp recordings to be obtained. Slice recording at the dialysis interface could be used to test the acute impact of ApoE and it's variants on synaptic physiology. Our findings have implications for the interpretation of ex vivo experiments assessing the effect of secreted proteins (e.g. ApoE, A-beta) on neurophysiology.

Neuroinflammation, peripheral immune cells and tau pathology in FTLD-tau.

Unique Code: TP001237

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Topic: Ageing and dementia

Background: Frontotemporal lobar degeneration (FTLD) is the pathological substrate of frontotemporal dementia (FTD) and is characterised by protein accumulation in the brain, with the most common form due to aggregated Tau (FTLD-tau). A potential role for neuroinflammation in FTLD has been highlighted by the discovery of genetic risk variants related to innate/adaptive immunity. Furthermore, studies have shown increased microglial and astrocyte activation together with T cell infiltration in the brain of a mouse tauopathy model (THY-Tau22).

Methods: To test the possible neuro-immune interactions in human FTLD-tau, we obtained FFPE brain tissue from 12 FTLD-MAPT, 33 Pick's Disease (PiD), 45 Progressive Supranuclear Palsy (PSP) patients and 55 controls. Using immunohistochemistry, we assessed the tau pathology across diseases using 8 antibodies directed against several sites of tau phosphorylation. Microglial markers were used to assess their immunophenotype and morphology (ramified, reactive, ameboid), while astrocytic phenotype and T cell infiltration exploration is currently ongoing. Results: Tau epitopes AT8, AT100, PHF1 and CP13 were increased in PiD, PSP and FTLD-MAPT compared to controls, with expression levels significantly correlated between tau epitopes. Microglial markers Iba1, CD68, HLA-DR and CD64 showed no difference between groups. However, CD16 was significantly increased in FTLD-MAPT vs. control ($p = 0.03$) and correlations between tau and microglial markers (except with Iba1) were detected between disease groups. Morphological assessment revealed that ameboid microglia were the highest represented population in PiD and FTLD-MAPT ($p<0.0001$ and $p<0.0001$, respectively); while reactive microglia were the most abundant population in PSP ($p<0.0001$). Preliminary observation of T cell staining confirms their recruitment in FTLD-tau.

Conclusion: These findings support the involvement of microglia in FTLD-tau. Additional immuno-phenotyping is necessary for further defining their role as well as T cell involvement in the disease pathogenesis.

Investigating tau propagation in neuronal networks

Unique Code: TP001238

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Topic: Ageing and dementia

The accumulation of insoluble neurofibrillary tangles, composed of hyperphosphorylated tau, is one of the main pathological hallmarks of tauopathies. Growing evidence indicates that tau misfolding and aggregation can propagate trans-synaptically along living and intact neuronal networks via 'prion-like' mechanisms (Clavaguera et al., 2009; De Calignon et al., 2012; DeVos et al., 2018; Hallinan et al., 2019). Importantly, tau can be released into the extracellular space under both physiological and pathological conditions and exist in diverse forms either as a free protein or vesicle-bound (Yamada et al., 2011, 2014; Pooler et al., 2013; Dujardin et al., 2014; Wang et al., 2017). Multiple secretion and re-uptake pathways have been suggested to play a role in the cell-to-cell spreading of physiological and pathological tau but the exact cellular and molecular mechanisms involved are still inconclusive (reviewed by Pernègre, Duquette and Leclerc, 2019; Brunello et al., 2020).

To dissect the release and re-uptake mechanisms of physiological and pathological tau in different tauopathies, we are taking advantage of sensitive bioluminescent assays, electrophysiological techniques, and orientated neuronal cell cultures in custom-made microfluidic devices (Holloway et al., 2019; Hallinan et al., 2020).

Two-way repeated measures ANOVA will be used to statistically compare the differences between experimental conditions at different time-points. Primary neurons derived from an individual donor animal are considered a biological repeat.

We predict that both pathogenic and physiological tau propagate trans-synaptically via distinct secretory and re-uptake pathways that are regulated by active cellular mechanisms. A greater understanding of the pathways involved in the release and re-uptake of extracellular tau species will help develop more effective therapies for tauopathies.

Does exercise affect neurovascular function in APOE-TR mice?

Unique Code: TP001242

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Topic: Ageing and dementia

Introduction

The APOE-ε4 (APOE4) gene is the most common genetic risk factor for the development of late-onset Alzheimer's Disease (AD). APOE4 is associated with cognitive decline during aging, vascular and blood-brain barrier dysfunction, early neuronal deficits and earlier plaque onset. Neurons require nutrients and oxygen to function, which are delivered to the brain via the blood flow. Changes in neuronal activity cause an increase in local blood supply, a phenomenon called neurovascular coupling (NVC). Previous findings from our lab suggest that NVC is impaired in APOE4-TR mice. Exercise is beneficial for the maintenance of vascular function. Therefore, exercise could improve the vascular deficits caused by APOE4.

Methods

A cranial window surgery is performed over the primary visual cortex (V1) of 9-week old APOE-TR mice of APOE3 or APOE4 genotype. Some mice are then provided with an exercise wheel in their home cage and some are prevented from exercise. Neuronal activation and vascular responses during presentation of a visual stimulus are recorded using two-

photon microscopy. Vessel diameter and red blood cell velocity (RBCV) changes are analysed and compared between genotypes and exercise conditions.

Approach for statistical analysis
The study comprises a total of N= 20 mice, with N=5 mice per group. A two-way ANOVA is used to determine if there is an interaction between exercise and genotype on the mean vascular values, where genotype (APOE3/4) and exercise (exercise/sedentary) are the independent variables. A Tukey posthoc test is performed to determine differences between each group.

Results
Preliminary results from the study show that sedentary APOE4 mice have reduced capillary and pia vessel diameter dilations in response to neuronal activation. However, APOE4 mice that have access to the exercise wheel show vascular function comparable to that of APOE3 mice. Furthermore, RBCV only partially increases upon neuronal activation in sedentary APOE4 mice, in contrast with what seen in active APOE4 mice and APOE3 mice.

Conclusions
We are successfully recording exercise behaviour and neurovascular responses in APOE3 and APOE4 mice. Present data suggest that exercise might rescue the vascular impairment seen in APOE4 mice.

TFEB and TFE3 biology and their regulation upon lysosomal biogenesis in an iPSC-derived dopaminergic neuron model of Parkinson's disease

Unique Code: TP001251
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Topic: Ageing and dementia

Introduction: Parkinson's disease (PD) is a neurodegenerative disease characterised by loss of dopaminergic neurons (DAns) in the substantia nigra, and α-synuclein aggregation. The autophagic-lysosomal pathway (ALP) is frequently considered a dysfunctional pathway in PD. Transcription factors EB/3 (TFEB/TFE3) play a crucial role in upregulation of autophagy and lysosomal biogenesis acting upon a gene network coined the 'Co-ordinated Lysosomal Expression and Regulation' (CLEAR) network. Building evidence describes therapeutic benefits of TFEB in PD. Little work has been done in a human-relevant model of PD, or on understanding therapeutic benefits TFE3 may provide against PD. Our work aims to characterise TFEB/TFE3 biology in iPSC-derived DAns (iPSC-DAns) and observe how they can be used to ameliorate ALP deficits in patient-derived iPSC-DAns.

Methods: Control and patient-derived iPSCs are differentiated into DAns using a common midbrain floor-plate protocol. TFEB/TFE3 expression and localisation, as well as CLEAR network regulation is assessed in iPSC-DAns. Autophagic flux and lysosomal function will be assessed following TFEB/TFE3 manipulation using different techniques such as: DQ-BSA and LysoPH, in iPSC-DAns derived from healthy individuals and PD patients.

Statistical analysis: Comparisons between treatments or TFEB/TFE3 expression is done using One-way ANOVA with multiple comparisons or Student's t-test, respectively. Public RNA-Seq data was processed using DE-Seq2 in R.

Results and conclusions: Through immunocytochemistry, RT-PCR, western blotting and RNA-Seq, we find TFE3 is strongly expressed in iPSC-DAns and TFEB appears absent. This is recapitulated through analysis of a publicly available RNA-Seq dataset of LCM-isolated human DAns, supporting the physiological relevance of this finding. Inhibition of regulatory kinases and lysosomal stress induction provokes nuclear translocation of TFE3 and subsequent upregulation of members of the CLEAR network despite TFEB absence. Our work will delve into how manipulation of TFEB/TFE3 and other MiT/TFE members in iPSC-DAns may increase lysosomal function and autophagic flux in order to ameliorate ALP deficits found in PD patient-derived iPSC-DAns.

Sleep disturbance and its association with histopathological Alzheimer's Disease and APOE-E4 genotype in individuals with and without dementia

Unique Code: TP001262

Authors: Jonathan Blackman - Neurosciences University of Bristol / North Bristol NHS Trust, Seth Love - Institute of Clinical Sciences University of Bristol, Lindsey Sinclair - Population Health Sciences University of Bristol, Elizabeth Coulthard - Bristol Medical School University of Bristol,

Topic: Ageing and dementia

INTRODUCTION

Alongside neuropathological change, sleep disturbance has also been demonstrated in Alzheimer's disease (AD) prior to the emergence of cognitive symptoms. Here we explore this relationship further, by studying the extent to which specific AD pathologies and stages in isolation may predict sleep disturbance. We analysed post-mortem histopathological findings in a cohort which had undergone extensive pre-mortem neuropsychiatric evaluation.

METHODS

This retrospective cohort study utilised UK Brain Banks Network data gathered with Medical Research Council support. Eligible subjects had pre-mortem Neuropsychiatry Inventory measures of sleep disturbance (NPIK), full pathological evaluation for Thal phase, Braak tangle stage and CERAD scores (measures of Aβ plaque distribution, tangle distribution and neuritic plaque density). Participants with other significant intracerebral pathologies were excluded. The full population was divided into groups with (AD+ve) and without (AD-ve) clinical AD dementia.

STATISTICAL ANALYSIS

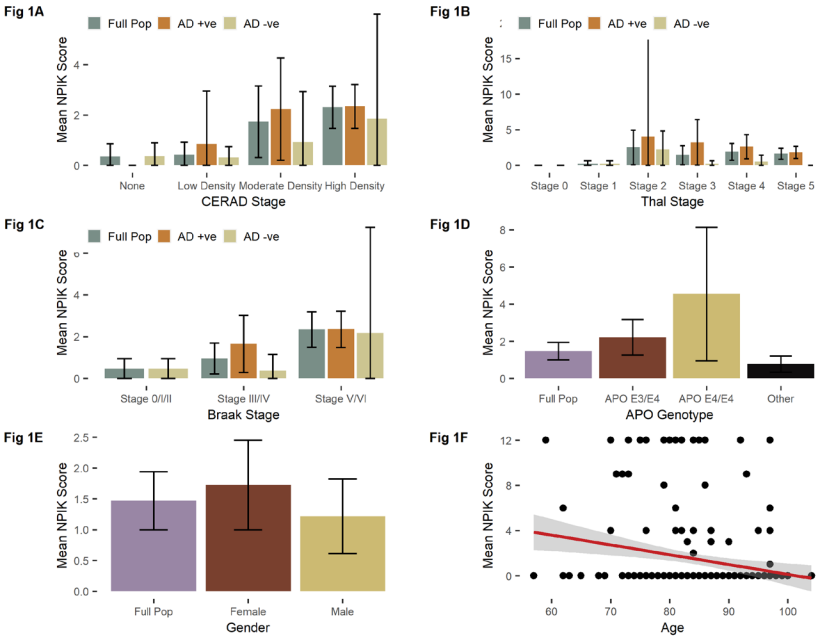
Stratified multivariate linear regression was performed across AD+ve and AD-ve groups with NPIK Global Score as the dependent variable. Dummy variables reflected each positive CERAD score, Thal phase and Braak stages I/II, III/IV and V/VI. Adjusted analyses controlled for confounders including age, gender and APOE ε4 status. Post-hoc analysis evaluated the relationship of APOE ε4 to sleep disturbance in the full population.

RESULTS

219 subjects met eligibility criteria, divided into AD+ve (n=123) and AD-ve groups (n=96). For unadjusted mean NPIK scores across modelled variables results see Figure 1. Thal phase 2 (hippocampal Aβ deposition) was associated with significantly higher NPIK scores in individuals without dementia (Est 2.15, p=0.005). APOE ε4 heterozygosity and homozygosity were independently associated with sleep disturbance after controlling for the extent of AD pathological change, CDR status, gender and age (Est 1.21, p=0.012) & (Est 2.76, p=0.020).

SUMMARY

Further exploration of associations of hippocampal Aβ plaques and the role of APOE ε4 may offer future mechanistic insights into sleep disturbance in AD.



ER Stress and Neuro-inflammation but no Presynaptic Loss Occur in Late-Stage Parkinson's Disease and Parkinson's Disease Dementia Patients

Unique Code: TP001273

Authors: Inga Schmidt - Translational Neuroscience University of Aberdeen, Amelia Dahlén - Translational Neuroscience University of Aberdeen, Maike Müller - Translational Neuroscience University of Aberdeen, Gernot Riedel - Translational Neuroscience University of Aberdeen, Bettina Platt - Translational Neuroscience University of Aberdeen,

Topic: Ageing and dementia

Parkinson's disease (PD) is characterized by the accumulation of α-synuclein and loss of dopaminergic symptoms. About 75% of PD patients develop dementia during the progression of their disease, categorized as Parkinson's disease dementia (PDD). Research on PDD has been mostly focussed on clinical aspects and is lacking in-depth post-mortem studies. The aetiology of PD vs. PDD remains elusive, though neuro-inflammation and ER stress have been proposed to aggravate the underlying processes.

In this study, post-mortem brain tissue of the temporal cortex originated from PD (n=8) and PDD (n=4) patients were compared to non-Parkinson's disease controls (NPC) (n=7), using Western blotting techniques.

PDD showed a trend of increased phosphorylated α-synuclein compared to PD, but no other differences were found. Interestingly, in PDD (vs PD) α-synuclein correlated stronger with eIF2α, indicative of ER stress particularly affecting memory function.

Interestingly, activated microglia (IBA-1) were increased by 72% in PD and by 27% in PDD while activated astrocytes (GFAP) were reduced by 41% in the combined PD and PDD group. GAPDH, a common house-keeping protein also linked

to apoptosis, was decreased in both PDD and PD by 71%. High amounts of oligomeric α-synuclein were negatively correlated to the ER stress marker eIF2a, which in turn was positively associated to a reactive tetrad of BiP, GFAP and GAPDH suggesting synergistic degenerative pathways that may be causally linked.

This data set forms a detailed analysis of associations between α-synuclein and other disease-relevant pathways, which have not been studied before, highlighting both differences and similarities of both PD and PDD. Further research is needed to understand the impact of these pathways and define causal markers of PDD pathology.

The effects of ageing upon cAMP response element-binding (CREB) proteins and differential protein expression in the CNS of Lymnaea stagnalis

Unique Code: TP001288

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Topic: Ageing and dementia

Introduction: With the increase of lifespan, age-related memory decline is affecting an increasing number of people. Although there is much known about neurobiological disorders, the molecular processes underlying memory decline during normal biological ageing are less well understood. Studies in vertebrates and invertebrates, including our research using Lymnaea stagnalis show that manipulation of CREB activity in old animals can lead to memory enhancement. However, much less is known about the dysfunction of CREB regulation related to ageing. Here we show that it is not the level of total CREB1 protein expression but rather the activation of the transcription factor by phosphorylation that declines with age.

Aims: To identify dysregulated pathways in ageing, total and phosphorylated CREB1 and CREB2 protein expression was measured and other proteins that are differentially expressed in young and old animals were identified.

Methods: Brains from 2-, 4-, 6- and 8-month-old animals were analysed using Western blotting (WB) and Liquid Chromatography-Mass Spectrometry (LC-MS).
Approach to Statistical Analysis: Statistical comparisons were made with Kruskal-Wallis one-way ANOVA analysis or Unpaired Student's t-test with Welch' correction. $P<0.05$ was considered statistically significant. All data are expressed as mean±SEM.

Results: WB results showed that phosphorylation of CREB1 significantly decreased with age (Fig. 1A). Total CREB2 was significantly decreased in all the older animals compared to the 2-month-old ones thus resulting in a significant increase of CREB1/CREB2 ratio (Fig. 1B). Among the proteins with differential expression between young and old animals (LC-MS), Fanconi anemia group M protein, involved in DNA repair and regulation of protein ubiquitination was increased. Histone-binding protein RBBP7, involved in negative regulation of gene expression; Adaptor Related protein Complex 3 Subunit Mu1, involved in protein sorting to the endosomal/lysosomal system were decreased with age (Fig.1C).

Conclusions: Age-related memory decline in Lymnaea is due to a decline in CREB1 activation by phosphorylation but not

due to a decreased CREB1/CREB2 ratio. Ageing in the brain dysregulates several interconnected pathways involved in memory formation.

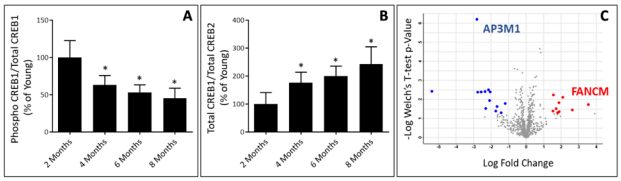

Figure 1: The effects of ageing on CREB transcription factors and global protein expression in the central nervous system of *Lymnaea stagnalis*. Brains from different age groups (2-8 months) were analysed using Western Blotting (WB) (A,B) and Liquid Chromatography-Mass Spectrometry (LC-MS; C). Ageing significantly decreased phosphorylation of CREB1 **(A)** and CREB1/CREB2 protein expression ratio **(B)** increased significantly with age. **(C)** Volcano Plot of protein expression in brains from 6- and 8-month-old snails. Coloured spots are indicating differentially expressed proteins (Blue: Down-regulated proteins; Red: Upregulated proteins. Among the differential expressed proteins, Adaptor Related protein Complex 3 Subunit Mu 1 (AP3M1), involved in protein sorting to the endosomal/lysosomal system, was found to be the most significant downregulated gene at 8-month vs. 6-month-old snails. Fanconi anemia group M (FANCM) protein, involved in DNA repair and regulation of protein ubiquitination, was found to be the most significant upregulated gene at 8 months vs. 6 months old snails. Results are expressed as mean ± SEM of 6 separate experiments. Asterisks indicate significance at at least P<0.05 compared to 2-month-old snails, based on unpaired t-tests with Welch's correction.

Effects of age-related changes in CNS lipid composition on serotonin release from the soma of a neuron involved in learning and memory formation

Unique Code: TP001290

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Topic: Ageing and dementia

Introduction: Age-related decline in cognition can be a consequence of subtle morphological and physiological changes in the brain. This can include changes in membrane lipid composition and neurotransmitter release. Therefore, exploring the contribution that age-related changes in membrane lipid composition make to serotonin release from a defined CNS neuron, the cerebral giant cell (CGC) that regulates feeding and long-term memory formation in the pond snail, would provide a better understanding of the underlying mechanism.

Methods: Carbon fibre microelectrodes with amperometric detection are utilised to measure the release of serotonin from the cell body of the CGC. CNS lipid composition is determined using high pressure liquid chromatography mass spectrometry.

Approach for statistical analysis: Serotonin release is recorded as amperometric events, which are analysed using IgorPro 6 routine from David Sulzer laboratory. Statistical analyses between groups are performed on the mean of the medians from each individual cell-recording using the appropriate statistical tests. Detection, identification and relative quantification of CNS lipids is achieved with the use of lipid standards and the LipiDex software suite and Student's t-test

or two-way ANOVA are used for comparisons.

Results and conclusions: Spontaneous or ionomycin-triggered events were recorded from both young and old CGC cell bodies. Ionomycin increased the number of release events in the young snails but was without effect in the old. Age significantly increased the half width, rise time and fall time and the number of molecules released per event. These changes correlate with an age-related increase in the concentration of cholesterol esters and sphingomyelin and decrease of phosphatidylinositol lipid in the CNS of Lymnaea. These data show age-related changes in the kinetics of somatic serotonin release from the CGC that, based on previous published work, are consistent with the observed changes in CNS lipid composition. Using drug manipulation of membrane lipids, we plan to demonstrate a causal relationship between the age-related changes in membrane lipids and vesicular release events and explore how this contributes to age-related deficits in learning and memory formation.

Impaired memory updating but intact change detection in early Alzheimer's disease: a Roving mismatch negativity task in MEG

Unique Code: TP001294

Authors: Ece Kocagoncu - Department of Clinical Neurosciences University of Cambridge, Melek Karadag Assem - Department of Clinical Neurosciences University of Cambridge, Juliette Lanskey - MRC Cognition and Brain Sciences Unit University of Cambridge, Anastasia Klimovich-Gray - Basque Center on Cognition, Brain and Language, Yun-Ju Cheng - Eli Lilly and Company, Andrew Quinn - Department of Psychiatry University of Oxford, Jemma Pitt - Department of Psychiatry University of Oxford, Vanessa Raymont - Department of Psychiatry University of Oxford, Richard N Henson - MRC Cognition and Brain Sciences Unit University of Cambridge, Mark W Woolrich - Department of Psychiatry University of Oxford, Anna C Nobre - Department of Psychiatry University of Oxford,James B Rowe - MRC Cognition and Brain Sciences Unit University of Cambridge,

Topic: Ageing and dementia

Introduction: There is an urgent need to develop reliable and sensitive biomarkers that help assess the efficacy of new therapeutic strategies for Alzheimer's disease (AD) at its prodromal stage of MCI. New Therapeutics in Alzheimer's Disease Project is a multi-centre, longitudinal, multimodal deep phenotyping study. It aims to develop and validate novel biomarkers sensitive to the pathophysiology of early AD, including synaptic dysfunction measured by electro-magnetoencephalography (E/MEG).

Methods: We have collected E/MEG and structural MRI data from healthy controls (N=15; MMSE M=29.4±0.74) and amyloid positive MCI and AD patients (N=46; MMSE M=24.8±3.37). E/MEG data was recorded during a Roving paradigm that measures change detection and sensory learning. Trains of repeating tones were played where the frequency and number of tones differed across trains. The difference between the first and sixth tone gave the mismatch response (MMN).

Approach for statistical analysis: We compared the time series as well as MMN amplitude in the frontal, temporal sensors and whole head, between groups. Test-retest reliability was measured with intraclass correlations. We tested the relationship between the MMN response, clinical severity and grey matter volume (GMV) using general linear models (GLM) correcting for age differences.

Results and conclusions: Both controls and patients showed strong early component of the MMN response between

100-200 ms. Controls showed a stronger, later component of the MMN response compared to patients, between 200-300 ms (P300). P300 showed high reliability in temporal gradiometers (ICC=0.73). GLMs revealed significant positive relationship between P300 and MMSE score, total and hippocampal GMV. Whilst the pre-attentive change detection, indexed by early MMN, remains intact, the later attention-dependent P300 response is significantly diminished in early AD. Diminished P300 response suggests a disruption in context-dependent updating of sensory expectations. P300 reductions correlated with clinical severity, and Alzheimer's related changes in GMV, confirming the clinical relevance and reliability of P300 in dementia research. Longitudinal data analysis is ongoing, to benchmark these E/MEG measures for clinical trials use.

ENDOSOMAL ESCAPE IS ESSENTIAL AND RATE-LIMITING IN THE SEEDED AGGREGATION OF TAU

Unique Code: TP001304

Authors: Benjamin Tuck - Department of Clinical Neurosciences University of Cambridge, William McEwan - Department of Clinical Neurosciences University of Cambridge, Taxiarchis Katsinelos - Department of Clinical Neurosciences University of Cambridge, Aamir Mukadam - Department of Clinical Neurosciences University of Cambridge,

Topic: Ageing and dementia

The transcellular propagation of tau is a major pathological event in Alzheimer's Disease (AD). The uptake of tau is well documented; however, the mechanistic understanding of how tau reaches the cytosol is poor. We propose the penetration of intracellular membranes as a rate-limiting factor in the transcellular propagation of tau. To investigate this hypothesis, we have established sensitive cell-based assays in immortalised cell lines and primary neuronal cultures that can quantify the entry of tau assemblies to the cytosol. We observed that tau assemblies are able to rapidly access the cytosol, reaching saturation within hours. Modifying entry via pharmaceutical intervention and genetic knockdown revealed endocytosis, but not other uptake pathways, as essential for the entry of tau to the cytosol ($p=<0.001$ one-way ANOVA when treated with endocytosis inhibitors). By interrogating the endo-lysosomal cellular machinery, we identified late endocytic vesicles as the primary escape compartment and we found that modifying the expression of AD genetic risk factors has a direct effect on tau entry ($p=<0.001$ one-way ANOVA when treated with late endosome GTPase RAB7A siRNA, or siRNA targeting AD-GWAS hits) . Importantly, the extent of entry determines the level of seeded aggregation observed. Our study identifies the penetration of endosomal membranes as a critical upstream step in the seeded aggregation of tau. The work so far demonstrates that contact between tau assemblies and native tau pools is rate-limiting and essential to seeded aggregation.

Ca2+ Cellular Compartment Specific Deficits In iPSC-Derived Neuronal Models of Parkinson's Disease

Unique Code: TP001310

Authors: Maria Claudia Caiazza - Department of Physiology, Anatomy and Genetics University of Oxford, Charmaine Lang - Department of Physiology, Anatomy and Genetics University of Oxford ,Richard Wade-Martins - Department of Physiology, Anat University of Oxford ,

Topic: Ageing and dementia

Aim and introduction: Parkinson's Disease (PD) is characterised by the loss of dopaminergic neurons (DAns) in the substantia nigra. Ca2+ is crucial in the regulation of many neuronal cellular processes. In particular, in DAns continuous Ca2+ waves occur, placing these neurons in an environment where even small alterations in Ca2+ homeostasis might impact on cellular function. We aim at studying the differences in Ca2+ dynamics in induced pluripotent stem cells (iPSC)-derived DAns from PD patients.

Methods and approach for statistical analysis: Here we utilise iPSC-derived DAns harbouring mutations in the GBA gene (GBA-N370S) and in the SNCA gene (SNCA-Trp). We employ Fura-2 to observe gross changes in Ca2+ dynamics and genetically encoded Ca2+ indicators (GECI) entrapped in the mitochondria and in the endoplasmic reticulum to trace down the source of such changes. Ca2+ imaging techniques are used in combination with drugs able to induce Ca2+ mobilisation in the cell to study Ca2+ dynamics in iPSC-derived DAns.

Comparison between genotypes was done using Student's t-test.

Results: iPSC-derived DAns harbouring the GBA-N370S and the SNCA-Trp mutations displayed altered Ca2+ dynamics. In particular, ionomycin-induced Ca2+ release in the cytoplasm appeared to be reduced. At a closer look, the ER appeared to release less Ca2+. At the same time, mitochondria displayed a decreased Ca2+ uptake in response to ionomycin. Finally, CCCP-induced Ca2+ release from the mitochondria was reduced in SNCA-Triplication neurons.
Further proteomic analysis will be carried out to investigate the origin of this dysfunction.
Conclusions: We believe that studying Ca2+ dynamics and deficits in iPSC-derived DAn models of Parkinson's could shed some light on the pathogenic mechanisms associated with neuronal vulnerability and death in Parkinson's. Mass spectrometry analysis will be employed to dig deeper into the causes of the calcium deficits described by studying the levels of Ca2+ transporters expressed in the ER and mitochondria of patients cells, with the ultimate goal to identify new therapeutic compounds that can be used to ameliorate early disease phenotypes, to halt the further downstream neurodegeneration as seen in Parkinson's.

Genetic variability associated with oligoadenylate synthetase 1, OAS1, in myeloid cells increases the risk of Alzheimer's disease and severe COVID-19

Unique Code: TP001316
Authors: Dervis Salih - IoN UK Dementia Research Institute at UCL
Topic: Ageing and dementia

Introduction:
GWAS of late-onset AD risk have highlighted the importance of gene variants expressed by the innate immune system. Recently we and others have shown genes that confer risk for AD are significantly enriched in transcriptional networks expressed by amyloid-responsive microglia. Identifying this transcriptional network allowed us to predict new risk genes for AD, including interferon-responsive oligoadenylate synthetase 1 (OAS1). However, the function of OAS1 within microglia and its genetic pathway were not known.

Methods:
Genotyping of SNP rs1131454 in control and AD human samples. Weighted gene co-expression network analysis of single-cell RNA-seq data from microglia of C57BL/6J and APP(NL-G-F) knock-in mice. Human microglial-like cells derived from iPSC (h-iPSC-Mg), were transfected with siRNA to knockdown OAS1 expression, and microglial status was assessed with quantitative RT-PCR.

Results and Conclusions:
We show SNP rs1131454 within OAS1 is associated with AD when we genotype 1314 people with AD and 1235 controls. The rs1131454 allele associated with increased risk for AD acts an eQTL and results in altered expression of the OAS1 gene in innate immune cells. Moreover, we see that SNP rs1131454 shows significant linkage disequilibrium with SNPs

recently identified to be associated with critical illness with COVID-19. By analysing single-cell RNA-seq data from isolated microglia in C57BL/6J and APP(NL-G-F) knock-in mice we identify a genetic network that is significantly upregulated with age, and with amyloid plaques, and contains the mouse orthologue Oas1a, suggesting an age-dependent function in the innate immune system. H-iPSC-Mg with knockdown of OAS1 expression and stimulation with interferon-gamma show an exaggerated pro-inflammatory response. Our data support a link between genetic risk for AD and susceptibility to critical illness with COVID-19, and that OAS1 coordinates the pro-inflammatory output of innate immune cells in response to elevated interferon levels. Understanding the mechanisms underlying this ageing-dependent genetic network containing OAS1 may aid development of treatments that benefit people with both AD and COVID-19, and may also allow us to develop biomarkers to track disease progression.

Alzheimer's and Parkinson's diseases predict different COVID-19 outcomes, a UK Biobank study

Unique Code: TP001319

Authors: Yizhou Yu - Toxicology University of Cambridge, Marco Travaglio - Toxicology University of Cambridge, Rebeka Popovic - Toxicology University of Cambridge, Nuno Santos Leal - Toxicology University of Cambridge, Luis Miguel Matins - Toxicology University of Cambridge,

Topic: Ageing and dementia

Introduction

In December 2019, a coronavirus, severe acute respiratory syndrome coronavirus 2 began infecting humans causing a novel disease, coronavirus disease 19 (COVID-19). Recent studies show that several medical conditions increase the risk of COVID-19 infection and death. The increased vulnerability of the elderly and those with comorbidities, together with the prevalence of neurodegenerative diseases, led us to investigate the links between neurodegeneration and COVID-19.

Method

We analysed the health records of 13,338 UK participants from the UK Biobank, who were tested for COVID-19 between March and July 2020. We fitted binomial regressions where the response variables were, respectively, COVID-19 positivity or COVID-19-related death. In all models, we accounted for a range of comorbidities including age, gender, social deprivation, number of people in the household, etc. We deposited the full analysis script on GitHub: github.com/M1gus/AD_PD_COVID19.

Results and conclusions

We first investigated the association between COVID-19 and multiple chronic conditions, and show that a diagnosis of dementia is associated with the largest increase in the odds of testing positive for COVID-19 (OR 3.25; 95% CI 2.73-3.87) (Figure 1A). This led us to analyse the association between dementia and COVID-19 death. We found that having dementia increases the odds of dying from COVID-19 by over 4 folds (OR 4.32; 95% CI 3.33-5.60) (Figure 1B). To improve the granularity of our analysis, we looked at different subtypes of dementia and found that a diagnosis of Alzheimer's disease (AD), the most common neurodegenerative disease, predicts a higher risk of COVID-19 infection (OR 4.15; 95% CI 3.22-5.34) (Figure 1C) and death (OR 4.17; 95% CI 2.87-6.05) (Figure 1D). This led us to look at the second most common neurodegenerative disease, Parkinson's disease (PD). Participants with PD were also at increased risk of COVID-19 infection (OR 1.74; 95% CI 1.34-2.27), but were not more likely to die from COVID-19. We conclude that there are disease-specific differences in COVID-19 susceptibility among patients affected by neurodegenerative disorders. Namely,

AD increases the risk of COVID-19 infection and death, while PD only increases the risk of infection

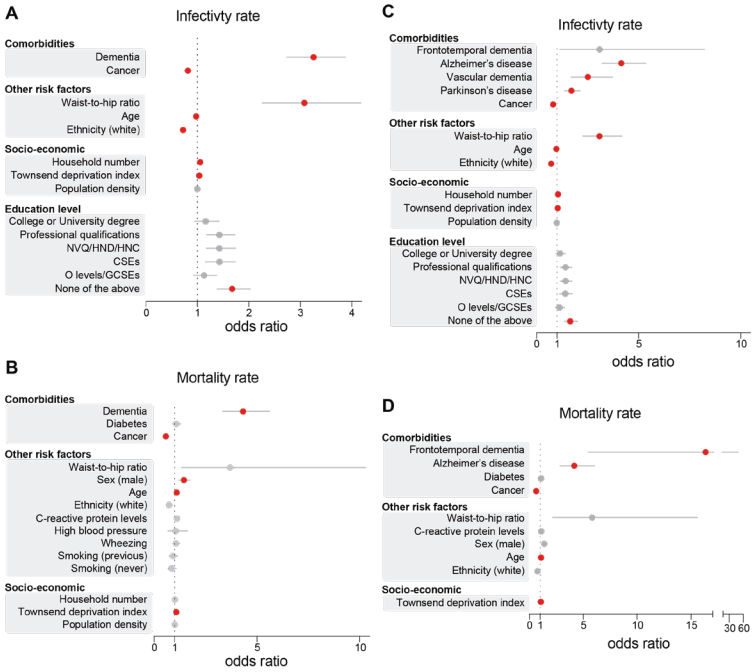


Figure 1. Dementia and Alzheimer's disease are the largest risk factor COVID mortality and infection. Odds ratios and respective 95% CIs for the relationship between individual-level characteristics and COVID-19 cases (A,C) or deaths (B,D). Red indicates significant associations ($p \leq 0.05$), while grey indicates a lack of significance ($p > 0.05$). The odds ratios for education levels are relative to A-levels. NVQ/HND/HNC, participants who received vocational qualifications such as National Vocational Qualifications (NVQ), Higher National Certificate (HNC) or Higher National Diploma (HND); CSEs, participants with a Certificate of Secondary Education (CSEs); O-levels/GCSEs, participants with either a General Certificate of Secondary Education (GCSE) or a General Certificate of Education (GCE) Ordinary Level (O-levels), a secondary school leaving qualification.

The influence of ApoE genotype on spatial memory and the hippocampal c-Fos response

Unique Code: TP001326

Authors: Alex Stuart - Neuroscience University of Sussex,

Topic: Ageing and dementia

Introduction:

Apolipoprotein E (ApoE) e4, but not e3, has been associated with an increased risk of Alzheimer's disease and cognitive decline. ApoE mouse models suggest age-related changes to hippocampal-dependent cognition and structure/function. In two experiments, we aimed to longitudinally map 'rapid-place learning' in ApoE-targeted-replacement (APOE-TR) mice across the lifespan and establish whether ApoE genotype influences hippocampal network activity in an age and behaviour-dependent manner.

Methods:

In experiment one, we trained APOE-TR mice (N = 36, e3/e4-TR) on a novel 'every-day learning' Barnes maze task. A longitudinal mixed design was used, assessing subjects from 3-21-months of age to track trajectories in spatial learning and memory. Presently, data collection has been completed for 3-9-months of age.

For experiment two, APOE-TR mice (N = 81, e3-e4/e3/e4-TR) were exposed to a novel environment or a home control

condition at 3 and 12-months of age. Hippocampal tissue was processed for c-Fos immunofluorescence to measure neuronal activity across the hippocampal axis or RT-qPCR to assess alterations in immediate-early gene activation.

Statistical analyses:
In experiment one, parametric mixed ANOVAs were used to analyse performance data as a function of ApoE genotype, age, and biological sex. Simple main effects analyses were used where appropriate for follow-up. A similar analysis design was conducted in experiment two, with the exception of using between-subjects ANOVAs.

Results and conclusions:
Experiment one revealed genotype and age specific alterations in rapid place learning ability, with e4-TR mice demonstrating a mild impairment at 3-months of age, but with matched performance to e3-TR controls at maturity (6-months). Continuing analysis will aim to establish performance profiles later in the lifespan.

In experiment two, female mice carrying e4-alleles showed a markedly higher number of active hippocampal neurons in several sub-regions. In the same samples, c-Fos mRNA levels were reduced with increasing number of e4-alleles in male, but not female, mice. These results were independent of behaviour, suggesting an e4-specific alteration in both basal hippocampal activity and the immediate-early gene transcriptional response.

The role of ubiquitin ligases Nedd4-1 and Nedd4-2 in the midbrain and their crosstalk with alpha-synuclein

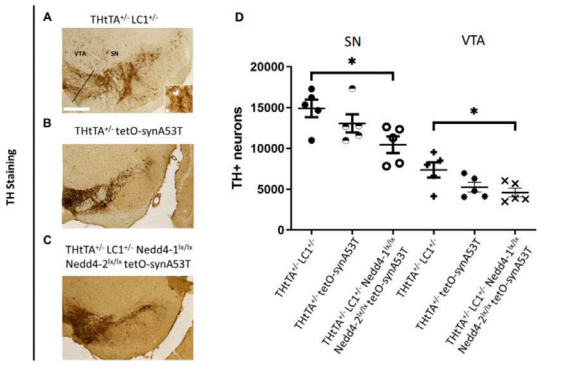
Unique Code: TP001345
Authors: James Conway - Peninsula Medical School University of Plymouth, Edgar Kramer - Peninsula Medical School University of Plymouth
Topic: Ageing and dementia

Parkinson’s disease (PD) is a progressive and currently incurable neurodegenerative disease and the most common disorder affecting movement. Intraneural aggregation of alpha-synuclein is thought to be an aetiological agent of PD, particularly when it accumulates in dopaminergic neurons, causing degeneration. Current PD treatments are symptomatic and do not target the disease at its source, or prevent its progression. Neural precursor cell-expressed developmentally derived 4 (Nedd4) is a family of E3 ubiquitin ligases shown in vitro to target alpha-synuclein for breakdown via ubiquitination.

It is therefore of interest to research the effect of deleting Nedd4 in vivo in dopaminergic neurons that die in PD. In order to confirm Nedd4’s endogenous role in the brain, we have generated mice in which two Nedd4 family members; Nedd4-1 and Nedd4-2 are deleted in dopaminergic (DA) neurons. The number of DA neurons and axons were quantified in the substantia nigra, ventral tegmental area and striatum in control mice as well as mice with Nedd4-1 and Nedd4-2 deleted. Cell bodies stained for tyrosine hydroxyls (TH) were quantified using unbiased stereology (Stereoinvestivator, MicroBrightField) and TH+ axon density by an automatic counting macro (Metamorph, Molecular Devices). Following statistical analysis by one-way ANOVA with Sidak's test for multiple comparisons, 12 month old mice with Nedd4-2 deleted in the dopaminergic system exhibit a reduced number of DA neurons and axons when compared to control animals. Our data suggest that Nedd4-2 has a role in the development and maintenance of the dopaminergic system.

To investigate the potential role of Nedd4 ligases in PD, we have also performed the same DA cell body and axon

quantifications in mice which have Nedd4-1 and Nedd4-2 deleted in addition to overexpressing the PD-relevant mutant form of alpha-synuclein (A53T). These mice exhibit a loss of DA neurons and axons compared to age matched control mice and A53T-only expressing mice (One way ANOVA with Sidak's test for multiple comparisons). This suggests an interaction of Nedd4 ligases with alpha-synuclein. With this information, molecular therapies may be developed to increase Nedd4 activity in PD patients to clear alpha-synuclein.



Double deletion of Nedd4-1 and Nedd4-2 enhances the alpha-synuclein-induced loss of TH+ neurons in the midbrain of 12 month old mice. A-C: Representative micrographs of THtTA+/- LC1+/- control (**A**), THtTA+/- tetO-synA53T (**B**) and THtTA+/- LC1+/- Nedd4-1fl/fx Nedd4-2fl/fx tetO-synA53T (**C**) coronal mouse midbrain sections. Large scale bar = 500µm. Arrowhead in small image indicates a TH+ neuron. Small scale bar = 50µm. **D:** Stereological quantification of TH+ cells in the Substantia Nigra (SN) and Ventral Tegmental Area (VTA) of 12 month old mice of indicated genotypes. Data plotted as mean ±SEM. Dots and crosses represent individual animal values. n= 5. $^{**}P \leq 0.05$, one way ANOVA with Šidák's test for multiple comparisons.

Posttranslational modifications of tubulin and microtubule associated proteins in Vascular Dementia and Alzheimer's Disease

Unique Code: TP001356

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Topic: Ageing and dementia

1. Introduction: Alzheimer's disease (AD) and vascular dementia (VaD) are the two most common forms of dementia in older people. Although they differ in their aetiology, they share pathophysiological features, such as tau and neuronal loss in the temporal lobe. Neuronal and synaptic loss are the best predictors for cognitive decline. In apoptosis, the cytoskeleton undergoes significant morphological changes due to the disruption of microtubules (MTs), the main protein of the cytoskeleton. MTs take part in a variety of functions; such as cell motility, shape, polarity, transport or mitosis. They are also essential for synaptic plasticity and their integrity and stability is crucial for proper neuronal functioning. Stabilization of MTs is achieved in different ways: through interactions with MT binding proteins (MTBPs) or by posttranslational modifications (PTMs) of tubulin. Some of these PTMs regulate the binding between MTs and MTBPs, and thus, play a role in neurodegeneration. We hypothesize that tubulin might undergo various PTMs, which hamper the binding to MTBPs and precede the observed tau and neuronal loss.

2. Methods: 37 samples of human brain homogenates - Controls (C n=13), VaD (n=13) and AD (n=11) – were analysed by Western Blot (WB). The levels of α3A1 and βIII tubulin (the most abundant tubulin isotypes in the brain) levels were measured, as well as several PTMs and MTBPs.

3. Approach for statistical analysis: for the statistical analysis, the One Way-ANOVA test was used, followed by a Tukey's

multiple comparison test.

4. Results and conclusions: We found that α3A1 tubulin is significantly increased in the temporal lobe of VaD, whereas βIII-tubulin is significantly decreased in AD. In addition, there was a decrease of detyrosination, MAP6 and MAP2 enzymes in AD, but not in VaD, showing possible diverse mechanisms of degeneration in both types of dementia.

A review of recent evidence for curcumin as a potential therapeutic agent for Alzheimer's disease, Parkinson's disease and Huntington's disease

Unique Code: TP001389

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Topic: Ageing and dementia

Introduction: Neurodegenerative diseases (NDDs) are characterised by pathological neuronal loss and progressive decline in nervous system functions, leading to often severe cognitive and physical disability and mortality. There is currently huge focus on developing new treatments for NDDs to not only treat symptoms but to address underlying mechanisms to slow or reverse neurodegenerative pathologies. Curcumin, an active hydrophobic phenolic compound, is a component of the spice turmeric and has a long history of use as a medicinal herb to treat a range of diseases. In this narrative review we review the recent evidence examining the potential therapeutic effects of curcumin in treating Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), focussing on human clinical trials and, if not available, cell and animal studies.

Methods: NCBI PubMed (https://pubmed.ncbi.nlm.nih.gov/) and NLM ClinicalTrials.gov (https://clinicaltrials.gov/) databases were used to identify relevant recent studies and clinical trials, using search terms including curcumin, Alzheimer's disease, Parkinson's disease, Huntington's disease, and associated terms (e.g. amyloid).
Approach for statistical analysis: Statistical analysis was not carried out for this narrative review due to the variety of data collected and the small number of analysed studies/trials.

Results and Conclusions: Curcumin improved cognitive, inflammatory or pathological markers related to AD in 67% (six of nine) of the studies involving humans that were analysed in this review. There have been no clinical trials or published studies using curcumin to treat PD or HD in humans. However, studies in animal and cell models of PD (seven studies) and animal models of HD (five studies) showed that curcumin protected neurons, reduced protein aggregation and inflammatory markers, and improved some symptoms in the animal models. This review highlights the potential usefulness of a widely available oral compound to combat severe NDDs. Important steps forward will include improving curcumin's bioavailability, longer and larger clinical trials on patients with AD, and the first trials in patients with PD or HD.

Recurrent urinary tract infections potentiate CD11b and GFAP white matter neuroinflammation in TgF344-AD rat

Unique Code: TP001390

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Topic: Ageing and dementia

Introduction: Neuroinflammation is increasingly recognised as a prodromal feature of Alzheimer's disease (AD). While familial AD is associated with endogenous neuroinflammation, whether recurrent systemic infections can potentiate neuroinflammation is underexplored. Systemic infections, such as urinary tract infections (UTIs), are known to increase risk of developing AD but whether certain brain regions are more prone to neuroinflammation following UTIs is unclear.

Methods: We used TgF344-AD rats aged 6- 12- or 18-months. We studied whether recurrent E. Coli UTIs, administered under anaesthesia to the bladder via catheter, could potentiate the expression of inflammatory markers CD11b and GFAP in white matter (corpus callosum and fimbria) and grey matter (medial parietal lobe), assessed via immunohistochemistry. We rendered 2D maximum intensity projections from tiled confocal panoramas (x&y: 380 µm, z: 10 µm). Iterative thresholding identified true positive labelling (ImageJ).

Approach for statistical analysis: We constructed three-way ANOVAs with age, genotype and UTI status as between-group factors and quantified the number of labelled cells and the percentage of pixels labelled as outcome measures.

Results and conclusions: CD11b+, but not GFAP+ labelling, was elevated in the TgF344-AD corpus callosum but not medial parietal cortex, vs. wild-type littermates at 6-months, prior to administration of UTIs. This trend increased at 12-months, with UTIs causing a large increase in CD11b+ and GFAP+ labelling in all three regions, with a larger effect in white matter. No further changes were observed at 18-months. These data provide evidence for prodromal CD11b associated neuroinflammation in white but not grey matter in TgF344-AD rat. Furthermore, UTIs at the age of early plaque formation potentiate CD11b and GFAP expression, with a greater effect in white than grey matter. Taken together, these findings suggest the TgF344-AD rat is a viable model of endogenous neuroinflammation in familial AD and indicate corpus callosum as a locus prone to a prodromal neuroinflammatory response stemming from prior systemic inflammation.

Circuit dynamics and oscillations

The Temporal Profiling and Modulation of Traumatic Stress Related Fear Memory Retrieval in a Rat Model of Post-Traumatic Stress Disorder

Unique Code: TP001053

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Topic: Circuit dynamics and oscillations

Post-traumatic stress disordPost-traumatic stress disorder (PTSD) is a complex syndrome, which may occur after life-threatening event. Fear memory abnormalities may play a vital role in this disorder. The review article by Do Monte et al.in 2016 indicated fear memories are not rigid; the retrieval of fear memory change over time. Furthermore, theta (4Hz) activities were found highly correlated with fear expression. However, the relation between the pathological fear

memory and potential brain wave features in PTSD still remains largely unknown. Here, we hypothesized that after traumatic stress exposure, the longitudinal dynamic changes of abnormal fears in PTSD animal models could be reflected by local field potentials (LFPs) measurements in early and late phases.

We use a well-established enhanced single prolonged stress (SPS&FS) PTSD rat model. Animals were restrained for 2 hrs and followed by 20 mins forced swimming, after that rats were exposed to diethyl ether until lose consciousness, foockshock was applied after awake for fear conditioning. We characterized brain wave features while context re-exposure with freezing behavior at early (10 mins, 30 mins, 2,4, 6 hrs) and late phases (day 1, 3, 7, and 14) after traumatic stress exposure. Behavioral results indicated SPS&FS rats showed comorbid PTSD phenotypes with significant higher anxiety, depression, anhedonia levels and impaired fear extinction. Time-dependent higher theta (5-8 Hz) and gamma (>30 Hz) observed only in 10 and 30 mins post SPS&FS and started to shift to continuous lower delta (0.5-4Hz) at 2hrs and maintained to D14. Besides, C-Fos protein labeling also indicated the temporal differences. For statistical comparison between groups (e.g. con v.s. SPS&FS), indexes of behavioral test and immunostaining were analyzed by one-way analysis of variance (ANOVA). Indexes of brain wave activity of specific time point, bandwidth and brain region were compared by two-way ANOVA, and all were further examined by post hoc Bonferroni t-tests, $p < 0.05$ were considered statistically significant.

The longitudinal profiling of abnormal fears with brain wave correlates may help illustrate the time-dependent pathological course in PTSD and may also help find better intervention strategies for this complex syndrome.

Investigating the hippocampal – medial prefrontal cortex circuit during NREM sleep in the APPNL-G-F mouse model of familial Alzheimer's disease

Unique Code: TP001122

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Topic: Circuit dynamics and oscillations

During NREM sleep, the hippocampal – medial prefrontal cortex (HPC-mPFC) circuit supports the long-term consolidation of our memories through temporal communication mediated by the oscillations found within these regions. The thalamocortical slow wave oscillation acts as a cardinal oscillator that nests faster oscillations such as gamma, spindles and sharp-wave ripples, facilitating the reorganisation of hippocampal memories to the cortex for long-term storage. Sleep disturbances are a key feature of prodromal Alzheimer's disease (AD) and there is evidence from both humans and rodents that several of the oscillations involved in the HPC-mPFC circuit are impaired. Yet very little is known about how this circuit is affected as a whole. Given the importance of the HPC-mPFC circuit in memory consolidation and that dementia is the main phenotype of AD, we aimed to investigate this communication using the novel APPNL-G-F mouse model of familial AD.

16-month-old APPWT and APPNL-G-F/NL-G-F mice were used. To record the neural activity of this circuit, mice were implanted with 4-channel microelectrodes (NeuroNexus) in the mPFC and dorsal CA1, with subsequent recording of natural sleep in their home cage during lights on. Signals were sampled at 30 kHz (bandwidth 0.1 – 7932.3 Hz) using an Open Ephys acquisition system. Offline analysis of signals was conducted using custom-made scripts in MATLAB.

Statistical analysis was performed using GraphPad Prism 9. In all cases, data were found not to be normally distributed.

Therefore, to compare the parameters collected during offline analysis with genotype, a Mann-Whitney U Test was used.

The power of the slow wave oscillation, delta and gamma oscillations did not differ between genotypes in either the mPFC or dorsal CA1. Interestingly, the amplitude and frequency of spindle events increased in the mPFC in APPNL-G-F/NL-G-F mice compared with APPWT but were found to decrease in dorsal CA1. Lastly, delta and spindle coherence between regions was not altered between genotypes. Taken together, this suggests that changes are occurring within the thalamic circuits generating spindle activity, whereas control over local oscillations and long-range communication is spared.

Spatiotemporal Analysis of Information Coding and Exchange in the Multiple Demand Network using fMRI-MEG Fusion

Unique Code: TP001130

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Topic: Circuit dynamics and oscillations

A multiple-demand network (MDN), composed of frontal and parietal cortices, is activated by, and encodes relevant information in, a wide variety of demanding cognitive tasks. They are proposed to select and integrate task-relevant information from across neural systems (Duncan et al. 2020) but the temporal dynamics of information processing and exchange remain unclear. For example, it is unknown whether information coding arises in sub-regions of the MDN one-after-another or simultaneously. Here, we used fMRI-MEG fusion to obtain spatiotemporal insight into information coding in the MDN during a cognitively demanding task. By comparing the temporal evolution of information (from MEG) to the information contained in different brain regions (fMRI), fusion can reveal the temporal order of information coding across regions. Then, to study the exchange of this information between regions, we developed a novel implementation of Granger-causality-based connectivity analysis using the estimated time-resolved response in each region. On each trial, one of four visual stimuli appeared (white squares on grey background; two in top-right and two in top-left hemi-fields), and participants (MEG: n=24; fMRI: n=30) had to press one of four buttons. They learned two orthogonal stimulus-button mappings (rules; indicated by fixation color) in a training phase. Using Representational Similarity Analysis, we fused four aspects of information: coarse stimulus (left vs. right stimuli), fine stimulus (inner vs. outer stimuli), rule and response information. Both coarse and fine stimulus information appeared first in posterior followed by anterior regions of the MDN. Rule information appeared in the same order. Parietal MDN was the region which showed the response information immediately before the response. Our connectivity analysis showed information transfer from sensory regions to MDN and its circulation within the MDN. Compared to other aspects of information, the fine stimulus information was most dominantly circulated within the MDN. These findings provide evidence for differential roles of MDN sub-regions across different information aspects. The new connectivity method opens opportunities for detailed study of information exchange with high spatial and temporal resolution.

Thalamic input in hippocampus, prefrontal and entorhinal cortices: absence of inputs into CA1 pyramidal cells

Unique Code: TP001195

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Topic: Circuit dynamics and oscillations

Interactions between medial prefrontal cortex (mPFC) and hippocampus are believed to underlie cognitive functions such as working memory. Impaired mPFC – hippocampal interactions are strongly implicated in cognitive impairments associated psychiatric disorders such as schizophrenia. Midline thalamic nucleus reuniens (NRe) acts as a hub to mediate prefrontal-hippocampal-entorhinal interactions, yet the cellular specificity of these connections remains unclear.

We have employed a an optogenetic circuit-mapping approach to determine how NRe mediates prefrontal information flow to hippocampal region CA1, using in vivo and in vitro electrophysiological methods. We used intracerebral injections of AAV vectors (AAV8-hSyn-Chronos-GFP and AAV8-hSyn-Chrimson-tdTomato) into NRe of Htr3a-GFP and Nkx2.1xTdTom mice to allow targeting of caudal or medial ganglionic eminence-derived inhibitory interneurons, respectively.

The neuronal subtypes and location were confirmed by post-hoc biocytin staining. Cortical areas were subdivided into layers and subiculum and prosubiculum were subdivided into shallow and deep layers. We measured input probability and AMPA/NMDA ratios to describe the cells connectivity from NRe to these regions. The differences in input from the NRe were statistically compared between regions and subregional locations.

Light stimulation of the opsin-expressing fibres evoked robust EPSCs in over 70% neurogliaform cells (n>70) but, remarkably, we failed to observe a somatic EPSC in CA1 pyramidal neuron. On the contrary, optogenetic activation of NRe projections to subiculum, medial entorhinal (mEC) and mPFC reliably evoked EPSCs in glutamatergic neurons. Neurogliaform cells had a distinctly higher AMPA/NMDA ratio of 3.05±0.13 SEM, when compared with principal responsive cells (0.53±0.06 for subiculum, 0.86±0.05 mEC and 0.24±0.01 mPFC).

NRe projections to the hippocampus proper appear to be highly selective for inhibitory interneurons, and either avoid or only sparsely target excitatory cells, in stark contrast to other regions targeted by NRe. Currently, we are focusing on determining the functional consequences of this unusual connectivity in vivo, and testing for a monosynaptic NRe to CA1 pyramidal cell connection via rabies virus-assisted tracing.

Noradrenergic inhibition within the Locus Coeruleus - A mechanism for modular interaction

Unique Code: TP001217

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Topic: Circuit dynamics and oscillations

The Locus Coeruleus (LC) has been shown to be a key mediator in a wealth of cognitive and behavioural states. In recent years, a multitude of studies have shed light on how sub-assemblies (modules) of LC cells with anatomically precise efferents underly this ability of the LC to interact with distinct brain areas, to bring about functionally distinct effects. However, the signalling mechanisms within the LC that facilitate this modularity remain unresolved. Here we present the results of experimental and computational work investigating the properties of alpha-2 adrenoceptor (α2R) mediated inhibition as both a negative feedback mechanism within the LC, and as a mechanism for lateral inhibition between LC modules.

We utilised a CAV-PRS-ChR2 vector to drive temporally precise spiking in LC cells in vitro, whilst recording from transduced & non-transduced cells to allow characterisation of auto- and lateral inhibitory responses to LC stimulation. This was performed in parallel with computational simulations of small populations of LC neurons using Hodgkin-Huxley formalism, and arranged in a reciprocally inhibitory modular structure.

We show that optogenetically evoked inhibitory transients (OEITs) are α2R mediated, outward potassium currents (mean amplitude 17.6±1.64pA, n=6 cells), with limited dependence on fast sodium conductances (Tetrodotoxin reduces the OEIT current to 73±5%, n=4 cells) . OEITs also show a non-linear frequency dependence, whereby stimulation at similar frequencies to tonic pacemaker LC activity (<10Hz) elicited small inhibitory responses, which increase steeply as stimulation frequency increased to ranges reflective of phasic activity bursts in the LC (20+Hz). This non-linear frequency dependence was replicated in computational modelling by addition of a 'synchronous' model of vesicular release, where noradrenaline release is facilitated by a calcium dependent exocytotic process.

This work fits within a growing literature on LC heterogeneity, and aims to provide additional evidence regarding the signalling pathways allowing interaction between anatomically defined LC modules. We will also discuss ongoing in vitro work utilising GCaMP6 imaging and chemogenetic activation of LC modules using retrograde CAV2-PRS vector

Hippocampal theta oscillations are the dominant network activity pattern during immobility in the ferret

Unique Code: TP001257
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Topic: Circuit dynamics and oscillations

Theta oscillations play a critical role in many hippocampal models of memory and spatial navigation. These models are based almost exclusively on rodent studies, and the impact of the specific ethological constraints of the rodent on hippocampal mechanisms is under debate. One hallmark of theta oscillations in the rodent hippocampus is the strong correlation with locomotor behaviours, however it has been recently suggested that rodent theta is instead associated with rhythmic sensory behaviours (i.e. whisking and sniffing). To further investigate the impact of sensory strategy and locomotor activity on hippocampal theta we performed hippocampal recordings in freely-moving ferrets. Ferrets are predatory carnivores with better spatial hearing and visual acuity than rats, while still sharing many other ethological similarities. We recorded hippocampal local field potential in rats and ferrets during comparable auditory/visual

localisation tasks designed to manipulate movement and sensory attention.

We have identified theta oscillations in the ferret hippocampus which occur at 3-7 Hz, a lower frequency band than commonly observed in the rat (5-12 Hz). In both species speed was the only behavioural variable that modulated theta activity. In the ferret theta oscillations robustly persisted during periods of immobility, contrasting starkly with large irregular activity in the immobile rat. Using pharmacological methods we identified this oscillation as Type II theta, a relatively rare phenomenon in the rat, which appears to be the dominant mode of the hippocampal network during immobility in the ferret.

Characterisation nematode acid-sensing ion channels (ASICs) and their role in rhythmic behaviour

Unique Code: TP001325

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Topic: Circuit dynamics and oscillations

Introduction: Protons can act as signalling molecules to modulate behaviour. Acid-sensing ion channels (ASICs) are members of the Degenerin/Epithelial Sodium Channel (DEG/ENaC) super-family conserved across species. Vertebrate ASICs have been proposed to function as synaptic proton sensors detecting subtle variations of extracellular protons. Here, protons act as modulators promoting synaptic plasticity and the formation of memory. Research in the nematode C. elegans has shown that proton signalling is not only restricted to synapses but that protons act as transmitters for motor contractions and rhythmic behaviour which is independent of the nervous system. C. elegans present an excellent model organism for a systems-level understanding of neural circuits and behaviour due to its complete connectome and recent advancements in the complete single cell RNA-Sequencing of every neuron class. Here we investigate the role of protons as signalling molecules to influence muscle contractions and behaviour.

Methods: Identification of nematode ASICs by ectopic expression in Xenopus oocytes. CRISP-Cas9 to generate mutants, microinjections of plasmids for generating transgenic animals. Testing behaviours that involve rhythmic muscle contractions (egg-laying intervals, defecation motor program oscillations).

Approach for statistical analysis: Descriptive statistics and inferential statistics (non-parametric Kruskal-Wallis, Dunn's multiple comparison test). For analysing the egg-laying intervals a software from the following paper was used (Waggoner et al., 1998) using a three-state model.

Results and Conclusion: We identified two groups of ASICs based on their response to neutral and low pH in vitro: One group is closed at neutral pH and becomes activated at low pH, and the other group is open at neutral pH and becomes blocked at low pH. Further in vivo characterisation of these channels show that they are expressed in neuronal and non-neuronal tissue. Mutants that lack these acid-sensing ion channels show abnormalities in rhythmic and motor behaviours. Based on this evidence we conclude the C. elegans acid-sensing ion channels regulate the general excitability of a wide range of cell types including muscle and epithelia, in addition to neurons.

Cognition and behaviour

Improved discrimination of similar contextual memories during episodic-like memory tasks in rats raised in an enriched environment

Unique Code: TP001040

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Topic: Cognition and behaviour

Episodic memories are multi-dimensional representations of past events, which often share similar contextual details. The hippocampus is thought to disambiguate between overlapping experiences via pattern separation, or the encoding of similar events using more dissimilar memory representations. Environmental enrichment (ENR) has been shown to improve behavioural pattern separation in several memory tasks, including contextual fear conditioning and spontaneous object recognition tasks. However, whether or how ENR improves episodic-like memory, involving an integration of different aspects of past experiences, remains to be investigated. Here, we found that young adult rats housed in an enriched environment for 4 months (enriched rats, N=12) outperformed standard-housed rats (N=12) in context-dependent associative recognition memory tasks, testing spontaneous recognition of novel object-context and object-place-context configurations. Critically, these effects were only found for similar, but not dissimilar, contexts, pointing to a selective ENR-dependent improvement in discrimination consistent with pattern separation. Moreover, enriched rats outperformed control rats in a spontaneous complex object recognition memory task, requiring the encoding of multiple distinct objects over a short period of time. Similar effects were not found when a single familiar object was used, nor when more time was given to encode the objects. Altogether, these results suggest that ENR improves complex recognition memory only when successful task performance is dependent on efficient pattern separation or fast encoding of novel information. Finally, previous studies suggest that ENR results in network changes within the hippocampal circuit, ranging from upregulation of adult hippocampal neurogenesis to increased sparseness of activity. Thus, we are currently assessing whether the ENR-dependent memory enhancements reported here are associated with altered levels of adult hippocampal neurogenesis and/or functional connectivity within the hippocampal-entorhinal network.

Social isolation and the neuroinflammatory response at different ages

Unique Code: TP001048

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Topic: Cognition and behaviour

Introduction: Social isolation is classified as a chronic mild stressor, which can lead to the development of neuropsychiatric disorders, including anxiety and depression[1-3]. Chronic stress can activate neuroinflammatory mediators in the central nervous system which are linked with the development of depressive disorders[4,5]. NLRP3 inflammasome activation integrates the stress-associated signals[6] and the consequent release of cytokine IL-1B is associated with a higher risk of depression[6]. Currently, there is a knowledge gap regarding neuroinflammatory

alterations induced by social isolation during both adolescence and old age periods. Therefore, this study aims to explore the effects of isolation on neuroinflammation in hippocampus region in both young and ageing male mice.

Methods: Young and aged C57BL7/J male mice were studied and divided into 2 groups: group housed (GH) and socially isolated (SI) for 3 weeks. Depression and anxiety were evaluated through Force Swim Test (FST) and Open Field (OF), respectively. Following the behaviour tests, molecular approaches were performed, specifically ELISA and Western Blot, to evaluate neuroinflammatory markers in hippocampus region, since they have a role in anxiety and depression.

Approach for statistical analysis: All the statistical analyses were performed with two-way analysis of Variance (ANOVA), with the housing conditions (group housed or social isolated) and aging (young and aged) as the between-group variables. Sidak was set as the post-hoc test. A $p < 0.05$ value was considered statistically significant.

Results and conclusions: Aged-SI mice showed depressive and anxiety-like behaviours during FST and OF, respectively. Microglia activation analyses demonstrated an increase of Iba-1 expression in Aged-SI group. Also, socially isolated groups displayed higher NLRP3 protein expression. Pro-inflammatory cytokine levels were higher in Aged groups. In summary, depressive- and anxiety-like behaviour was observed, as well as a neuroinflammatory response due to social isolation, in aged mice.

Basal amygdala defines hippocampal output via cell-type specific targeting of long range excitation and inhibition

Unique Code: TP001049

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Topic: Cognition and behaviour

The projection from the basal amygdala (BA) to ventral hippocampus (vHPC) is crucial for the appropriate behavioural response to both positive and negative stimuli. However, the circuit mechanisms by which it carries out this role remain unknown. In particular it is unclear how BA input to vHPC promotes reinforcing responses. Using anatomical tracing and ChR2-assisted circuit mapping, we found evidence for both monosynaptic excitatory and inhibitory input from BA that targets distinct projection populations in the vHPC (Wilcoxon paired test, $p < 0.05$). By modelling this circuit we found that the presence of long-range inhibitory input from BA changes the output of vHPC to favour activation of neurons that project to the nucleus accumbens. Consistent with these circuit findings, using a combination of in vivo optogenetic and chemogenetic manipulation during behaviour, we found that coactivation of both excitation and long range inhibition is reinforcing and that this activity is dependent on vHPC-NAc projecting neurons (two-way ANOVA; interaction between group and drug, $p < 0.05$). Overall, we show that the BA projection to vHPC is composed of both long-range excitation and inhibition. These projections differentially connect with the different projection cell types in vHPC, and the balance of these two pathways determines the behavioural consequences of BA to vHPC activation.

Language processing across childhood and adolescence: an fNIRS study

Unique Code: TP001059

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Topic: Cognition and behaviour

Functional and structural neuroimaging have shown that language networks mature during normal development. However, a detailed timeframe of these developmental changes in language processing is still lacking. Therefore, in typically developing school-aged children we investigated receptive and expressive language processing using functional near-infrared spectroscopy (fNIRS).

Specifically, 30 healthy native English speakers (12 children, age range: 6 to 10 years old and 18 adolescents, age range: 11 to 16 years old) were recruited. Neural activity was measured bilaterally over frontal and temporal areas using fNIRS while participants completed computer-administered language tasks.

A mixed ANOVA showed a statistically significant interaction between hemisphere (left and right), region (temporal and frontal) and age group (children and adolescents) ($F(1,24) = 4.317$, $p < .05$), and thus the simple effects for the two groups were examined. Paired samples t-tests within the adolescents' group showed a statistically significant difference between mean neural activity over the left temporal region and the left frontal regions ($t16 = 2.817$, $p<.05$) which was independent of task performance. However, no differences were found in the children's group.

Overall, these findings suggest that language processing within the left hemisphere continues to develop into adolescence, perhaps reflecting an automation in language skills that is yet to mature in younger children. Further studies with a larger sample size and longitudinal design are needed to confirm this conclusion. These findings will inform the design of future studies investigating neural markers of language maturation in children with atypical language development.

Establishing a Role of the Semantic Control Network in Social Processing: a Meta-analysis of Functional Neuroimaging Studies

Unique Code: TP001060

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Topic: Cognition and behaviour

A core question for the cognitive sciences concerns how we flexibly interact with others and coordinate behaviour to achieve mutually beneficial outcomes. The present study aims to shed light upon the cognitive control or regulatory systems that shape the way we interpret and respond to social interactions. Despite a general acceptance of the importance of control mechanisms for social competence, most leading models of socio-cognitive processing devote very little discussion to the precise nature and neuroanatomical correlates of their involvement. Recently, however, it has been proposed that a set of regions specialised for the controlled retrieval and selection of semantic information, namely the inferior frontal gyrus (IFG) and the posterior middle temporal gyrus, plays a key role in social cognition. We, therefore, set out to investigate whether the distributed neural activation commonly found in social functional neuroimaging studies extended to these regions. To this end, we conducted five large-scale coordinate-based meta-analyses to combine the results of over 500 independent fMRI/PET experiments using the Activation Likelihood Estimation approach. We identified the neural networks reliably involved in semantic control, as well as four social abilities, including theory of mind, trait inference, empathy and moral reasoning. This allowed an unprecedented parallel review of the neural networks associated with these cognitive domains. We observed that the left IFG (pars orbitalis) region involved in semantic control is reliably engaged in all four of the social domains. We found additional overlap between brain regions involved in semantic control, theory of mind, trait inference and empathy, specifically in the

supplementary motor area and the right IFG. This finding supports the proposal that the neurocognitive system dedicated to the controlled retrieval and selection of conceptual knowledge is involved in the processing of social information and has implications for models of both neurotypical and disordered social cognition.

Effect of maternal high fat diet consumption during preimplantation and gestation/lactation on mouse offspring locomotor behaviour & cognitive ability

Unique Code: TP001065

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Topic: Cognition and behaviour

Foetal impairments in offspring brain. We hypothesise, in the absence of obesity, a maternal high-fat diet (HFD) consumption during gestation/lactation or only during the preimplantation-period may still affect offspring behaviour and brain function.

After conception, female MF1-mice were divided into 3 groups: embryonic HFD (EHFD) group, (mothers were fed with HFD only during first 3.5 days of their pregnancy); HFD and control (CFD) groups (mothers were fed with HFD and chow-diet, respectively, throughout pregnancy/lactation periods). To evaluate locomotor and exploratory-like behaviours of offspring, open field test was conducted for 10min at 4 and at 10 weeks old. The parameters, like resting time, jump counts, rearing counts were obtained with the ENV250 software, and compared for the first-5 and last-5min of the tests. To evaluate their working memory, a T-maze test was performed at 8 weeks old. One-way ANOVA following with post-hoc Bonferroni test or Kruskal- Wallis H test in SPSS was used to evaluate the differences of variables within the offspring.

In adolescence, at 4 weeks old, males did not show any significant differences between diet groups, in both halves of the test for any of the OFT-parameters. Similarly, females did not show any significant differences between the diet groups in the first 5min for any of the parameters. However, in the last 5min, EHFD females significantly jumped less and rested more compared to CFD females. In adulthood, at 10 weeks old, EHFD males showed significantly reduced rearing compared to CFD males in both halves of the test. Similarly, the rearing of EHFD females was significantly decreased compared to CFD females in the first 5min. T-maze alternation scores of EHFD males were significantly higher than CFD males while there were no differences between females.

EHFD offspring exhibited altered locomotor, explorative behaviour and working memory while HFD offspring were no different from control. This data with a limited number of litters shows the preimplantation period is vulnerable to maternal HFD in the absence of obesity.

Inadequate parental care activates nestling stress physiology without impairing spatial learning or hippocampal neuroplasticity in adult zebra finches

Unique Code: TP001076

Authors: Michael Emmerson - School of Biological & Chemical Sciences Queen Mary University of London,

Topic: Cognition and behaviour

Inadequate parental care during early-life exposes young animals to adverse experiences (e.g. malnutrition and sub-optimal temperatures) that cause short-term stress physiology activation (e.g. raised glucocorticoid levels). Such early-life adverse experiences have long-term effects on neurocognitive phenotypes, including reduced hippocampal neuroplasticity markers (e.g. BDNF) and impaired hippocampal-dependent cognitive abilities (e.g. spatial learning). Such effects are reliably reported in response to maternal abandonment in uniparental mammalian species, but the effects of inadequate early-life parental care in biparental species (e.g. from losing one parent or the presence of more siblings diluting parental care) are unclear. Here, we used biparental zebra finches to explore the effects of inadequate early-life parental care (via removal of one parent or brood enlargement) on nestling stress indicators (growth rate, surface temperature, glucocorticoid concentration) and, in adulthood, spatial learning abilities and hippocampal neuroplasticity markers (e.g. BDNF). General linear models were used for all statistical analyses, with experimental condition entered as a fixed factor in all models and age entered as a repeated measure for growth and temperature models. Nestlings raised by single parents or in enlarged broods had slower growth rates and elevated glucocorticoid levels compared to controls, but surface temperatures were similar in all birds. Adult spatial learning abilities and hippocampal neuroplasticity were also similar in all birds. Our results show that inadequate parental care in biparental species that falls short of complete parental abandonment is not sufficiently adverse to impair neurocognitive phenotypes and further emphasise the importance of species-typical parental care systems when assessing the development of cognitive abilities and their neurophysiological correlates.

Serotonin depletion impairs both Pavlovian and instrumental reversal learning in healthy humans

Unique Code: TP001077

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Topic: Cognition and behaviour

Serotonin is implicated in aversive processing and updating responses to changing environmental circumstances. Optimising behaviour to maximise reward and minimise punishment may require shifting strategies upon encountering new situations. Likewise, emotional reactions to threats are critical for survival yet must be modified as danger shifts from one source to another. Whilst numerous psychiatric disorders are characterised by behavioural and emotional inflexibility, few studies have examined the contribution of serotonin in humans. We modelled both processes in two independent experiments (N = 97; 50 females, mean age 24), using instrumental and aversive Pavlovian reversal learning paradigms, respectively. Upon depleting the serotonin precursor tryptophan – in a double-blind randomised placebo-controlled design – ANOVA revealed healthy volunteers showed impairments in updating both behaviour (F(9,603) =

2.024, p = .035, ηp2 = .029) and emotion (F(1,26) = 17.604, p = .00028, ηp2 = .404) to reflect changing contingencies. Reversal deficits, furthermore, were correlated with the extent of tryptophan depletion in both the instrumental (r(66) = -.311, p = .011) and Pavlovian domains (r(27) = -.536, p = .004). These results translate findings in experimental animals to humans and have implications for the neurochemical basis of cognitive inflexibility.

Two parallel output populations in ventral hippocampus have distinct roles in decision making under uncertainty.

Unique Code: TP001078

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Topic: Cognition and behaviour

Ability to make flexible decisions under uncertainty is extremely important and impairments in this process have been associated with a number of psychiatric conditions.

To investigate the neural substrates and mechanisms of the decision making under uncertainty we used probabilistic reversal learning task in mice. While traditionally it has been viewed as a simple value updating problem, recently it has become clear that animals use knowledge of the task structure to infer the hidden states and guide their decision making. In this paradigm, for optimal performance it is necessary to continuously integrate past trial outcomes to predict the state transitions to new reward contingencies associated with different actions following the reversal.

Recent evidence points at hippocampal circuitry as anatomical basis for solving this complex problem. The ventral part of the hippocampus (vH) is formed of parallel and largely non-overlapping populations of neurons that project to multiple regions including the prefrontal cortex (PFC) and the nucleus accumbens (NAc). To explore the role of the vH circuitry in decision making we selectively inactivated neurons in vH in mice during probabilistic reversal learning. Using one-way ANOVA and Tukey post hoc tests, we found that bilateral optogenetic silencing of either PFC- or NAc-projecting vH neurons significantly impaired animals' performance in the task. Our data suggest that inactivation of different projection populations had distinct effects on animals' decision making by either altering their sensitivity to action outcomes or changing how animals utilise the predictions when making decisions.

Overall, we showed that vH circuitry is important for integrating past experience to predict the outcome of future actions and to guide the decision making under uncertainty. Ongoing work is investigating the circuit and functional basis of how vH projections influence the VTA during decision making.

On the same Wavelength: Assessing Interpersonal Neural Synchrony in Parent-Child Dyads using fNIRS Hyperscanning

Unique Code: TP001090

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Topic: Cognition and behaviour

During social interactions, we must establish an emotional connection as well as swiftly and accurately infer each other's goals and intentions. The temporal alignment of behavioural, physiological, and neural signals (i.e. bio-behavioural synchrony) plays a vital role in this process. Here, our research focussed on the temporal alignment of neural signals (i.e. interpersonal neural synchrony; INS), and its relation to interaction success and quality in parent-child dyads.

N=108 parent-child dyads (N=42 mothers; child age 5-6 years) underwent functional near-infrared spectroscopy (fNIRS) hyperscanning during cooperative versus independent problem-solving and rest. Dyads completed two 2-minute puzzle-solving sessions per condition with three 80-second resting phases in between. Task performance was measured by the number of puzzles solved. The procedure was videotaped and coded regarding interaction success and quality. Parents also self-reported on stress and parental involvement. Brain activity was recorded in parents and children at bilateral dorsolateral prefrontal cortex (DLPFC) and temporo-parietal junction (TPJ). Wavelet transform coherence (WTC) was applied to assess the relation between the two fNIRS time series.

INS was assessed as a function of experimental condition and region of interest and related to behavioural and self-reported variables using linear mixed models in R with appropriate HSD correction for multiple comparisons (where applicable). To rule out INS effects due to spurious correlations, additional random pair analyses with 1,000 permutations were conducted.

We observed increased INS in bilateral DLPFC and TPJ during cooperative versus independent problem solving and rest across all parent-child dyads. Yet, INS somewhat differed between mother- and father-child dyads. Task performance, behavioural interaction quality, and self-reported parental stress were only associated with INS during cooperation in mother-child dyads. In father-child dyads, there was a positive relation between self-reported parental involvement and INS during cooperation. These data show that INS plays an important role during social interaction in parent-child dyads albeit with somewhat different functional roles, which warrants further investigation.

The natural manifestation of working-memory use

Unique Code: TP001094
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Topic: Cognition and behaviour

Working memory (WM) is a fundamental cognitive function which supports tasks that require bridging between perception and subsequent behaviour. Highly controlled laboratory tasks have been used to investigate its properties, such as its capacity. We know much less about the utilisation of WM in natural behaviour, that is when reliance on working memory emerges as a natural consequence of interactions with the environment. We tracked head, hand, and eye movements during an adapted object-copying task, during which participants copied a model display by selecting realistic objects from a resource pool and placing them into a workspace. Our task enabled us to derive an implicit measure of the tradeoff between reliance on working memory and gathering information from the external world during natural behaviour. By further manipulating the locomotive demands required for task completion, we could investigate whether and how WM utilisation changed as gathering information from the environment became more effortful. Mixed-effects models were used for the statistical analysis. Reliance on WM was much lower than predicted based on WM capacity measures in typical laboratory tasks. As sampling information from the environment required increasing locomotion, participants relied more on their WM representations. This reliance on WM increased in a shallow, but linear fashion from ~1 to an average of ~2 features in memory. Encoding more features was associated with

longer encoding durations, which made the individual copying sequences last longer. Nevertheless, using memory improved performance as it enabled more information to be copied in each sequence, which reduced the overall completion times of the to-be-copied displays. But this increase in efficiency plateaued at ~2 to 3 features in memory. Our results showcase a fundamental dependence on external information during ecological behaviour, even if the potentially storable information is well within the capacity of the cognitive system. These findings highlight the importance of investigating how the use of cognitive processes unfolds within natural tasks and extend our understanding of the interplay between memory and perception in immersive behaviour.

Forgetting rates of gist and peripheral episodic memory traces in prose recall

Unique Code: TP001101

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Topic: Cognition and behaviour

Introduction: In a seminal study, Slamecka and McElree (1983) showed that the degree of initial learning of verbal material affected the intercepts but not the slopes of forgetting curves (i.e. the curves were parallel). However, more recent work (Sekeres et al., 2016) has reported that memories for central events (gist) and memory for secondary details (peripheral) for film clips were forgotten at different rates over periods of days, with gist memory retained more consistently over time than details. By adapting the experimental design devised by Slamecka and McElree (1983), the present experiments aimed to investigate the differences of gist and peripheral episodic memory traces for prose passages over long-term intervals of up to a month.

Methods: In a series of three experiments, a total of 232 participants listened to two short prose narratives with a fixed balanced score for gist and peripheral memory. At different time delays, free recall performance was scored according to criteria for recall of gist and recall of peripheral details. In the first two experiments participants were tested repeatedly after 1 to 5 days and a month, while in the third experiment they were tested only after a month.

Approach for statistical analyses: analyses were carried out with generalised linear mixed modelling as implemented by the lme4 package in R.

Results and conclusions: Across the three experiments, memory for gist was higher than for peripheral details which were forgotten at a faster rate over a month, with or without the presence of intermediate recall at shorter intervals. Repeated testing had a significant benefit on memory for both gist and peripheral details. These findings suggest that the strength of episodic memory traces on initial learning plays a role in long-term forgetting.

Slamecka, N. J., & McElree, B. (1983). Normal forgetting of verbal lists as a function of their degree of learning. Journal of Experimental Psychology: Learning, Memory, and Cognition, 9(3), 384-397.

Sekeres, M. J., Bonasia, K., St-Laurent, M., Pishdadian, S., Winocur, G., Grady, C., & Moscovitch, M. (2016). Recovering and preventing loss of detailed memory: differential rates of forgetting for detail types in episodic memory. Learning & Memory, 23(2), 72-82

Investigating the role of CYFIP1 and CYFIP2 in numerosity

Unique Code: TP001103

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Topic: Cognition and behaviour

INTRODUCTION

The ability to discriminate discrete numbers of items has been widely reported in both humans and non-human animals. Numerical abilities provide ecological advantages leading to the hypothesis that numerosity (the ability to assess number) is evolutionarily conserved (Tosto et al, 2014). Dyscalculia is a human syndrome which has the phenotype of reduced specific numerical abilities (Landerl et al, 2004). Poor numerosity is also associated with genetic syndromes including Fragile X syndrome (FXS) and Prader–Willi Syndrome (PWS). The Cytoplasmic FMR1-Interacting Protein (CYFIP) gene is highly associated with both FXS and PWS and was found to be in the top 10% of hits in GWAS studies for dyscalculia (Chen et al, 2017). Previous studies have explored the phenotype of CYFIP1 and 2 mutants in mice and zebrafish, but never in respects to numerical abilities. Here we tested the role of CYFIP 1 and 2 in number cognition using zebrafish behavioural analysis.

METHODS

CRISPR/Cas9 genome editing was used to generate loss of function mutant zebrafish lines for both CYFIP 1 and 2, with NOGO decay qPCR used to validate the loss of function through the reduction of mRNA. The numerical abilities of the zebrafish were assessed using an established group size preference (GSP) assay (Sheardown et al, unpublished) using 28-33 days post fertilisation (dpf) zebrafish.

APPROACH FOR STATISTICAL ANALYSES

All molecular and behavioural data was checked for normality and analysed using ANOVA in SPSS 27.

RESULTS AND CONCLUSIONS

Heterozygous loss of function mutants with significantly reduced mRNA levels were generated for CYFIP 1 and 2 using CRISPR. Wildtype fish robustly show a significant preference for the larger group when presented with 5v2 in the GSP assay. Both CYFIP 1 and 2 have significantly reduced performance and do not show any preference. This suggests that CYFIP 1 and 2 have a role in the numerical abilities of zebrafish, giving further evidence for their role in human dyscalculia.

LSD reduces hippocampal- cortical interactions in freely moving rats

Unique Code: TP001109

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Topic: Cognition and behaviour

Hallucinogens including lysergic acid diethylamide (LSD) produce false percepts disjoint from the external environment. Despite increasing interest in using these drugs therapeutically, their effect on neural activity is largely unknown. Hippocampus (HC) and visual cortex (VC) contribute substantially to the construction of an internal map of the external world. As such, we employed in vivo electrophysiology recordings of neurons in CA1 of HC and VC while rats ran on a familiar track for food (PRE and POST) after the administration of a saline injection prior to the PRE session and either a control or LSD for the POST session. The control included saline, a 5HT2A receptor antagonist M100907 with LSD, or M100907 alone. LSD produced a dissociative-like state manifesting in high voltage spike local field potential activity in cortex during immobility on the track while hippocampus quieted compared to the typical sleep-to-wake transition ($P = 0.0039$, Wilcoxon signed rank test), but not under the control ($P = 0.25$). Furthermore, during running under LSD, CA1 and VC displayed reduced coactivity. For each pair of CA1-VC cells active during running, we computed a normalized cross-correlogram relative to those computed from the shuffled spikes of the two cells. Visualizing these correlograms, coactivity in PRE and POST occurred under all conditions, but with a smaller peak under LSD. We then computed a Pearson's correlation between coactivity values in PRE and POST for all active pairs to find that the correlation was significantly smaller under LSD compared to control ($P = 2.1 \times 10\text{-}11$, Fisher's exact test) suggesting dampened coactivity between the regions with LSD. Additionally, hippocampal place cells retained their spatial information during running in PRE and POST under LSD ($P = .46$, Mann-Whitney test), but had reduced firing rates between PRE and POST under LSD ($P = 9.8 \times 10\text{-}22$, Wilcoxon signed rank test). Place cells also displayed reduced directional specificity only in the LSD condition in POST, determined by comparing spatial correlations between a cell's rate curves on the two opposing trajectories in a session ($P = 0.017$, Mann-Whitney test). We demonstrate that VC and HC uncouple with reduced coactivity following LSD administration and altered firing rates. This miscommunication may contribute to the observed degraded representations of the environment in hippocampus and give insights into LSD-produced abnormal perceptions.

Vestibular Agnosia Linked to Widespread Abnormality of Functional Brain Networks

Unique Code: TP001111

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Topic: Cognition and behaviour

We recently reported a new condition - 'Vestibular Agnosia' - where acute TBI (aTBI) patients failed to perceive vertigo despite a manifest vestibular-ocular reflex (VOR) activation. In aTBI patients, vestibular agnosia was linked to impaired postural control via white-matter damage in the right inferior longitudinal fasciculus. Here we investigate the link between vestibular agnosia and resting state functional connectivity in aTBI, independent from postural control, and hence identify the brain regions specifically linked to self-motion perception. We assessed the functional differences revealed by analysing grey and white matter separately, using independent component analysis (ICA) and regions of interest (ROI). In 39 aTBI patients with intact peripheral and reflex vestibular function, we assessed self-motion perceptual thresholds during passive yaw rotations in the dark and analysed the scans of 25 aTBI patients following quality control. Using normative self-motion perceptual thresholds of 37 healthy controls, we classified 11 aTBI patients with vestibular agnosia (VA+) and 14 without vestibular agnosia (VA-). Grey-matter specific ICA showed that VA+

patients compared to VA- had: (i) decreased functional connectivity in right intracalcarine cortex in a resting state network composed of superior and mid temporal regions; (ii) increased functional connectivity in the left frontal pole in the rostral prefrontal cortex resting state network. White-matter specific resting state ICA showed that VA+ patients (vs. VA-) had increased functional connectivity in the right superior longitudinal fasciculus and right posterior thalamic radiation. ROI-to-ROI white matter specific analyses revealed a bilateral white matter network with increased functional connectivity in VA+ vs. VA-, with all connections originating from left anterior corona radiata. In conclusion, vestibular agnosia results in widespread abnormal white matter functional networks while grey matter functional changes are more specific to putative vestibular resting state networks, presumably reflecting low-order sensory processing. Abnormal prefrontal resting state networks could reflect abnormal perceptual 'ignition' of self-motion sensation.

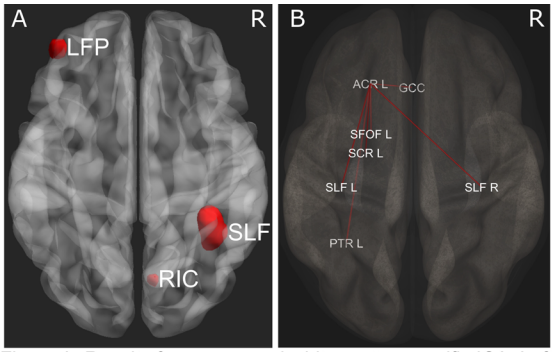

Figure A: Results from grey- and white-matter specific ICA. Left frontal pole (LFP; MNI: -42,48,00) and right superior longitudinal fasciculus (SLF; MNI: 39,-51,06) had increased while right intracalcarine cortex (RIC; MNI: 6,-72,12) had decreased functional connectivity in VA+ compared to VA-. Figure B: Group of connections in white matter specific ROI analysis showing increased connectivity in VA+ compared to VA- patients; connections originating from left anterior corona radiata (ACR) and terminating at right and left SLF, left posterior thalamic radiations (PTR), left superior corona radiata (SCR), genu of corpus callosum (GCC), and left superior fronto-occipital fasciculus (SFOF).

Reduction in grid cell regularity is associated with changes in distance estimation in rats

Unique Code: TP001114

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Topic: Cognition and behaviour

Grid cells in the medial entorhinal cortex (MEC) fire in a regular hexagonal grid pattern as an animal passes through its environment – providing a putative measure of distance travelled that could be used for path integration. The firing pattern of grid cells has been shown to warp in polarized environmental geometries such as trapezoids, suggesting that path integration should be impaired. The present study made in-vivo electrophysiological recordings from grid cells in MEC in rats performing a distance estimation task. Rats (n=4) were trained to run a specific distance in a rectangular box. The box was then transformed into a trapezoid and the rats required to estimate the same distance. Consistent with previous studies from our group, a paired samples t-test revealed that distance was consistently over-estimated in trapezoidal relative to rectangular environments. Grid cells were defined statistically relative to a distribution of grid scores produced using shuffling-analysis of rotational symmetry. Statistical comparison (repeated measures ANOVA) of gridness scores in the two environmental geometries revealed that grid cells were significantly less regular in the trapezoid compared to the rectangle. Interestingly, grid regularity did not immediately return to normal in the rectangle

session following the trapezoid sessions suggesting that distortions in the grid pattern caused by altering environmental geometry take some time to be reset. These data are consistent with grid cell regularity being necessary for distance estimation.

Dopaminergic modulation of learning from social and individual information

Unique Code: TP001115
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Topic: Cognition and behaviour

Whether (social) learning from other people is underpinned by the same, 'domain-general', mechanisms underpinning learning from one's own experience (individual learning) has been the subject of considerable debate. For existing dissociations between social and individual learning, social information often comprises an 'indirect source' that can be used to supplement one's own, 'direct', experience. Thus, learning source (social/non-social) and directness (indirect/direct) are often confounded. We recently argued that social and individual learning can be dissociated at a neurochemical level along the directness, but not the learning source axis (Cook et al, 2019), with effects of dopamine manipulation on adaptation to environmental volatility observed for the direct learning source only. Here we tested this idea further. On two separate days, participants ingested 2.5mg Haloperidol, a dopamine D2 receptor antagonist, or placebo, and completed a probabilistic learning task which demanded learning from two sources (social, individual). The 'direct' condition featured social as the direct (and individual as the indirect) learning source, the 'indirect' condition featured social and the indirect (and individual as the direct) source. A mixed-effects model with fixed factors drug, learning source, volatility (volatile, stable) and group (social-direct, social-indirect), and random intercepts for subject, was employed to test our hypothesis that Haloperidol would affect direct-learning irrespective of its social/non-social nature. Results showed an effect of drug along the social but not directness axis, with haloperidol having dissociable effects on learning from social and individual information. Specifically, under haloperidol, subjects showed more adaptation to the current state of environmental volatility for social information and less for individual information. Results provide preliminary evidence for the existence of domain-specific neurochemical signalling mechanisms for social learning.

Cook et al, 2019. eLife 2019;8:e51439 DOI: 10.7554/eLife.51439

Recreational Drug Use and Prospective Memory

Unique Code: TP001125
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Topic: Cognition and behaviour

Prospective memory (PM) impairment in recreational drug users has been documented in recent years. However, most studies on the effects of drugs on PM contain several methodological challenges, such as small sample size (<100 participants), unrepresentative sample type (e.g., student or patient), short abstinence period (<7days), and lack of control of potential confounds (e.g., sleep, IQ etc.). The present study investigated the possible consequences of recreational drug use on prospective memory, using self-report and lab-based prospective memory measures while overcoming the methodological challenges. The sample was composed of 47 non-users (27 females, age range from 18

to 50+) and 53 drug-users (21 females, age range from 18 to 50+). Non-parametric tests were used as all the variables were not normally distributed. Mann-Whitney U was used to determine if the means of two groups were significantly different from each other.

In order to control for covariates, Quade's rank analysis of covariance (RANCOVA) was used. Recreational drug users reported significantly more deficits in the Long-term Episodic, Short-term Habitual and Internally cued PM failures subscales of the Prospective Memory Questionnaire. However, these deficits were eliminated after controlling for covariates (e.g., sleep quality, general health, alcohol usage). Recreational drug users also performed worse than non-users in the Short-term, Long-term, Event-based and Time-based PM subscales of the Royal Prince Alfred Prospective Memory Test. These results remained significant after controlling for the covariates. Drug users demonstrated greater impairments on time-based and long-term PM tasks thought to be linked with executive functioning. Taken together, the present study provides further support for recreational drug-related deficits in PM and highlights a dissociation between self-report and lab-based PM measures.

Activation of the amygdala and bed nucleus stria terminalis after detection of ambiguous threat cues by rats

Unique Code: TP001137

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Topic: Cognition and behaviour

Introduction

Hypervigilance, a state of sensitivity to threatening stimuli, is an attentional bias symptomatic of many anxiety disorders. As such, this research intends to develop and refine a rodent test of hypervigilance that could be used to screen new therapeutics. This work characterises the brain basis of the vigilant-like behaviour.

Methods

Rats were trained in a fear-conditioning procedure, in which a tone predicted an unavoidable footshock. Ultrasonic vocalisations and freezing were measured across conditioning and a subsequent test. Additionally, the CS was modified at test to increase its ambiguity, by modifying the predictability and salience, in order to screen for hypervigilance. Inter-individual differences in anxiety-related behaviour was examined. Immunohistochemistry was also performed to establish the brain regions activated, by measurement of cFos expression, with the expression of freezing and/or vocalisation in the 22kHz range (ultrasonic alarm calls).

Approach for statistical analysis

In order to analyse the effects of group (training schedule or test volume, depending on the experiment) and CS presentation on freezing repeated measures two factor ANOVAs with post hoc Sidak correction tests were performed. Across brain region analysis of cFos expression was analyses using ANOVA. Between groups levels of cFos were

compared using an independent samples, two-tailed t-test. Further investigation into the association between freezing and cFos levels were conducted were correlated using Pearson's correlation coefficient. Statistical significance was taken to be at $P<0.05$.

Results and conclusions
A drop in salience reveals individual differences in vigilance to a threat cue. The relation of hypervigilance to extinction, and reacquisition of fear are currently being investigated. A 50% drop in reinforcement ratio was not sufficient to significantly reduce associability as measured at test.

The most anterior BLA and also the BNST were activated by threat cues (relevant to NAc). The activation of more lateral BNST sub-regions, fusiform and oval nuclei, negatively correlated with freezing. The BLA was activated to an equivalent extent despite a change in saliency or in predictability.

Two opposing hippocampus to prefrontal cortex pathways for the control of approach and avoidance behaviour

Unique Code: TP001142
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Topic: Cognition and behaviour

The subiculum is the main output region of the hippocampus. Despite targeting multiple downstream regions, its efferents are thought to be organised as parallel projections, with any one neuron targeting only one downstream region. Here, we focus on the projection from the ventral subiculum to the prefrontal cortex (PFC). The ventral hippocampal-prefrontal pathway is involved in the production of a range of behaviours including working memory, aversive learning and anxiety, and its dysfunction is linked to key aspects of several psychiatric disorders.

Through anatomical, electrophysiological and morphological investigation of the ventral hippocampal-prefrontal pathway, we found that the hippocampal projection to prefrontal cortex is composed of two parallel circuits located in the superficial or deep hippocampal pyramidal layers. These circuits have unique upstream and downstream connectivity, and are differentially active during exploration of a potentially threatening environment. The superficial population is preferentially connected to widespread PFC inhibitory interneurons, while the deep circuit is connected to PFC pyramidal neurons and fast spiking interneurons. Artificial activation of the superficial circuit promotes exploration via preferential recruitment of PFC inhibition, while activation of the deep circuit promotes avoidance via direct excitation. Together this provides a mechanism for regulation of behavior during approach avoidance conflict: through two specialised, parallel circuits that allow bidirectional hippocampal control of PFC.

The relationship between experimenter-scored and participant-scored measures of mental time travel: Discrepancies between the past and future

Unique Code: TP001146
Authors: Lucie Reed - Psychology Cardiff University, Dr Lisa Evans - Psychology Cardiff University,
Topic: Cognition and behaviour

Introduction: Experimenter-scored and participant-scored measures are both used to assess mental time travel. However, there is a lack of knowledge about the relationship between these two measures and thus whether they

correspond. To address this gap in the literature, we investigated whether the autobiographical interview (AI) scoring system (Levine et al., 2002) correlates with participant-scored ratings.

Methods: Participants (n = 52) were presented with various cue words to prompt discussion of past and future events. Their responses were recorded and scored according to the AI scoring subcategories. Participants rated each event for vividness (1= not vivid, 7= very vivid), as well as event/perceptual, spatiotemporal, and emotion/thought details (1= not at all clear, 7= extremely clear and distinct).

Approach for statistical analysis: To assess the relationship between AI scoring and participant ratings, several Spearman's correlations were computed. We expected to see significant correlations between the AI scoring and related participant-scored subcategories (i.e. event/perceptual, spatiotemporal, emotion/thought) as well as the total number of internal details and participant-scored vividness.

Results and conclusions: For past events, no significant relationships were found between the AI scoring and participant-scored subcategories. For future events however, significant relationships were found between the emotion/thought subcategories as well as the total number of internal details and self-reported vividness. Given the striking similarities between remembering the past and imagining the future, these differing results were surprising. Overall, our findings demonstrate the complex relationship between participant-scored and experimenter-scored measures of mental time travel.

Extinction of Appetitive Memories: Behavioural Profile and Neural Mechanisms

Unique Code: TP001150
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Topic: Cognition and behaviour

In appetitive Pavlovian conditioning, an initially neutral cue (conditioned stimulus, CS) is paired with the delivery of a reward (unconditioned stimulus, US) via associative learning. Once the CS-US associative memory is established, CS presentations alone elicit a variety of conditioned responses (CRs) in the anticipation of reward delivery. Repeated or prolonged non-reinforced presentation of CSs weakens CRs though a process called extinction. Extinction of fearful associations has been previously thoroughly studied. However, an important but understudied area is regards to the extinction of associative memories involving an appetitive US. The aim of the present research was to investigate the behavioural and neural underpinnings of extinction of Pavlovian appetitive memories.

To study the behavioural profile of appetitive extinction, rats were trained in a Pavlovian conditioned approach (PCA) paradigm, in which a compound light+lever CS is paired with food delivery. Probability to lever press/nosepoke, number of contacts with CS lever/food magazine, and latency to approach CS lever/food magazine during training sessions were recorded and subsequently used for calculation of a PCA index. PCA index, ranging from -1 to 1, is used to classify animals as sign-trackers (ST, predominantly interacting with CS cue) or goal-trackers (GT, showing preference towards the site of reward delivery).

We found that three days of PCA training lead to the development of two distinct conditioned approach strategies in rats – sign-trackers vs goal-trackers. Unrewarded CS-presentations extinguished Pavlovian conditioned approach

responding, by reducing both behavioural strategies. Also, we investigated the role of NMDA-type glutamate receptor (NMDAR)-dependent neurotransmission in appetitive extinction, using systemic administration of MK-801 (selective and non-competitive NMDAR antagonist). We observed that PCA extinction is disrupted by systemic MK801 administration, suggesting that NMDARs are necessary for acquisition/consolidation of the appetitive extinction memory.

Noradrenergic loss contributes to apathy in Parkinson's disease through the precision of expected outcomes

Unique Code: TP001151

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Introduction

Apathy is a common and debilitating feature of Parkinson's disease (PD), but its underlying mechanisms remain poorly understood. We propose that cell loss in the locus coeruleus (LC) and consequent depletion of noradrenaline (NA) contributes to apathy. We present a new model of apathy in the context of the Bayesian brain framework, where actions require predictions of their outcomes to be held with sufficiently high precision. We previously showed that apathy is associated with reduced precision of prior beliefs about action outcomes, leading to a failure of active inference (Hezemans et al., 2020, J Exp Psychol Gen). Here, we tested the hypothesis that the apathy-dependent prior weighting is moderated by the LC-NA system in PD.

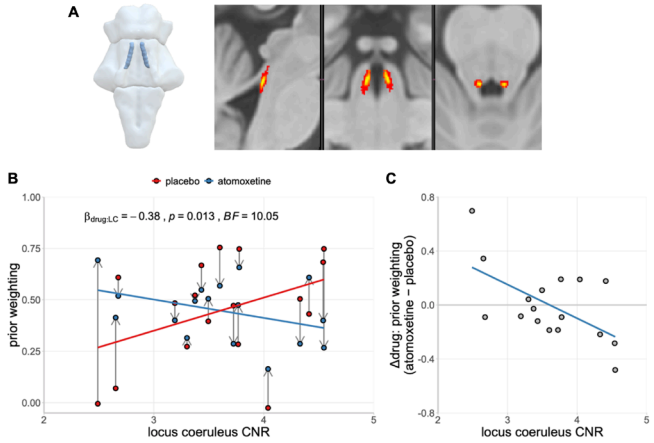
Methods

Participants with PD (N=17) completed a randomised, placebo-controlled, double blind, cross-over study with a single 40mg dose of the NA reuptake inhibitor atomoxetine. We administered a visuomotor task that involved effortful, goal-directed behaviour, and required participants to estimate their own performance. Age- and education-matched controls (N=20) performed the same task without the drug manipulation. We estimated LC integrity using an advanced magnetisation transfer weighted sequence at ultra-high field (7T), with atlas-based segmentation for LC localisation and signal quantification (Ye et al., 2021, NeuroImage).

Approach for statistical analysis

The relationship between participants' estimated and veridical performance was used to infer prior weighting (relative precision). The effects of atomoxetine, LC integrity, and their interaction on prior weighting were estimated by linear mixed models.

Results and conclusions
The effect of atomoxetine on PD patients' prior weighting varied strongly as a function of LC integrity. Specifically, patients with a more degenerate LC benefitted more from treatment by atomoxetine. The noradrenergic effects on prior weighting may help explain dopamine-insensitive symptoms in PD, including apathy. This study supports a Bayesian account of apathy that can help understand individual differences, and predict potential individual benefits from noradrenergic treatment.



The Cortisol Effects on Brain Activity and Cognition Study (CEBAC Study): An fMRI study of emotional face processing and pulsatile cortisol dynamics

Unique Code: TP001152

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Topic: Cognition and behaviour

Cortisol is the primary human stress hormone and is a glucocorticoid (GCC) produced by the HPA axis, an important neuroendocrine system. Cortisol production follows both circadian (~daily) and ultradian (~hourly) rhythms, and this rhythmicity, known as pulsatility, is believed to be essential for healthy neurological and physiological function. Previous work from our group indicated that changing GCC dynamics alter emotional face processing. The CEBAC Study was designed to discern the importance of the different phases of cortisol pulsatility on the functional neuropsychology of healthy volunteers whose natural cortisol rhythm was suppressed and replenished pulsatile cortisol infusion (n=20 for behaviour, n=16 for imaging). Participants in this study completed an fMRI study which included a novel emotional processing task, the Facial Expression Ambiguity Resolution Task (FEART) and resting state scans, on 3 occasions: (i) during the rising phase of an elevated cortisol pulse (15 mg; within physiological range), (ii) during the falling phase of

this pulse and (iii) following 15 hours cortisol suppression without replenishment. The FEART used a 4 (session: baseline cortisol training (no imaging), cortisol rising, cortisol falling, vs cortisol suppression) x 2 (run: run 1 vs run 2) x 2 (ambiguity: low vs high) x 2 (emotion type: anger/fear faces vs sadness/fear faces) within-subjects design. Behavioural measures of accuracy and response times indicated that participants performed better (with greater accuracy and faster responses) for low ambiguity trials compared to high. Furthermore, they showed poorer accuracy but faster responses in the cortisol falling session compared with the cortisol rising session. Whole brain imaging analysis showed an interaction effect of session and ambiguity level (high > low ambiguity, in cortisol rising > cortisol falling) with enhanced activation in the lateral occipital cortex, occipital fusiform, occipital pole, temporal pole, inferior frontal gyrus, orbitofrontal cortex, and frontal operculum cortex: areas associated with visual and emotional processing. Together, these behavioural and imaging findings, support the hypothesis that cortisol dynamics play a role in facial expression ambiguity resolution in the human brain.

Evidence against effects of surprise on memory for preceding elements in the same event

Unique Code: TP001154

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While most of our daily experiences are forgotten, we tend to have strong memories for experiences that take us by surprise. Extensive research has backed this intuition, demonstrating people are more likely to remember surprising moments than ordinary ones. However, this research has tended to focus on the surprising elements themselves, and less is known about how a surprising element affects memory for the surrounding event in which it occurred. If events are encoded as cohesive units, the benefit of surprise would be expected to spread to preceding elements in the same event. In contrast, if each element is encoded independently, memory for preceding elements would be unaffected.

To test this, we presented 340 participants (online) with a set of stop-motion films. The films were designed such that actions could be replaced with surprising ones without altering the rest of the film, enabling us to test whether surprise exerts retroactive effects on memory. Each target scene had two versions (with/without surprise), and was preceded by a neutral scene, allowing us to test whether any retroactive effects would be confined to the same event. Participants' memory for actions in the film was then probed either immediately or 24h later.

The study was run with a Bayesian sequential design, collecting data in batches until a stopping criterion was reached or up to a predefined maximal number of batches. The stopping criterion was based on a 3-way Bayesian ANOVA with a within-subject factor of surprise (whether a target scene was surprising), a within-subject factor of action-type (whether the tested action was in the target scene or the preceding one) and a between-subject factor of delay. Specifically, it was defined as evidence (Bayes Factor >=6) in favour of: 1) a main effect of surprise, 2) a surprise/action-type interaction, or 3) a 3-way interaction – or evidence against all three.

We found evidence against all three, indicating that surprise did not modulate memory for preceding events – neither when participants were tested immediately after study nor 24 hours later. We suggest two accounts for these findings: 1) elements of an event are encoded independently, or 2) that surprise segments experience, sectioning off the preceding elements as a separate event.

Prefrontal neural disinhibition and functional inhibition does not impair object recognition memory

Unique Code: TP001159

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Neural disinhibition, or reduced GABA activity, in the prefrontal cortex has been implicated in the pathophysiology of schizophrenia (Lewis et al., 2012, Trends Neurosci.). Neural disinhibition has also been suggested to underlie the novel object recognition (NOR) deficits found in rodent models of NMDA receptor (NMDAR) hypofunction (Cadinu et al., 2018, Neuropharmacology). Here, we investigated whether local neural disinhibition of the rat medial prefrontal cortex (mPFC) by the GABA-A receptor antagonist picrotoxin would result in NOR deficits similar to those through NMDAR hypofunction; for comparison, we also examined the impact of local functional mPFC inhibition by the GABA-A receptor agonist muscimol. Previous findings suggest that the perirhinal cortex is critical for NOR, whereas, the mPFC is not required (Warbuton & Brown, 2015, Behav. Brain Res.); however, the mPFC projects strongly to the perirhinal cortex (Deacon et al., 1983, J. Comp. Neurol.). Therefore, we hypothesised that mPFC neural disinhibition would disrupt NOR, via aberrant drive of projections to the perirhinal cortex (compare Bast et al., 2017, Br. J. Pharmacol.), whereas, NOR would be intact following mPFC functional inhibition.

Young adult male Lister hooded rats were tested on the NOR task using a within-subjects design following local microinfusion of saline (0.5 µl/side), picrotoxin (300 ng/0.5 µl/side) or muscimol (62.5 ng/0.5 µl/side) into the mPFC (Pezze et al., 2014, J. Neurosci.). The NOR task, adapted from Pezze et al. (2017, Learn Mem.), consisted of 3-min acquisition and retrieval phases, separated by 1-min retention delay spent in the home cage. Data were analysed by ANOVA, using infusion condition and object (novel vs. familiar) as within-subject factors. Rats showed a clear novel object preference across all conditions, with no difference between conditions (Fig. 1).

Neural disinhibition in the mPFC did not result in a NOR deficit, suggesting that prefrontal GABA function is not required for NOR memory. Furthermore, our results support the conclusion that NOR deficits following NMDAR hypofunction cannot be directly attributed to reduced GABA function in the mPFC.

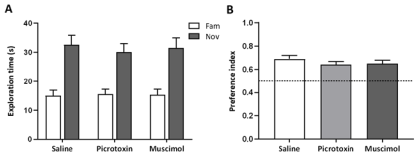

Fig. 1. ***Local neural disinhibition and functional inhibition of the mPFC, caused by microinfusion of picrotoxin and muscimol, respectively, does not impair NOR memory.*** **A.** Exploration times (s) of a familiar (Fam) and novel (Nov) object during the 3-min retrieval phase in the NOR test, following a 1-min retention delay in the home cage. In all infusion conditions, rats spent more time exploring the novel vs. familiar object, reflecting intact NOR memory. Planned pairwise t-tests confirmed this difference was significant across all conditions ($t_{13} > 4.5$, $p < 0.001$). ANOVA revealed a main effect of object type ($F_{(1, 13)} = 64.54$, $p < 0.001$), without a main effect or interaction involving condition ($F_{(2, 26)} < 1$). **B.** Preference for the novel object (time spent exploring novel object/total time spent exploring both objects). Preference index (PI) confirmed that rats in all infusion conditions preferentially explored the novel object, with performance differing from chance (PI = 0.5, indicated by dotted line) in all conditions ($t_{13} > 5.3$, $p < 0.001$, one sample t-test). ANOVA revealed no main effect of condition ($F_{(2, 26)} < 1$). Data are shown as mean (±SEM), n = 14, within-subjects design.

Does your gaze affect my memory? Investigating the gaze cuing effect in virtual reality

Unique Code: TP001167

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Topic: Cognition and behaviour

Using a simple gaze cuing task, where an onscreen face looks towards or away from an objects eventual location, it has been found that validly cued (looked at) items are processed faster, liked more, and remembered better. It is hypothesised that this gaze cuing effect occurs because the social context afforded by the gaze cue enriches the experience. However, it is currently unclear if these effects can be found in a more realistic environment. Here, we further investigated the influence of another person's gaze on visual working memory using virtual reality (VR). Realistic human avatars (4 male, 4 female) were presented (individually) sat at a table. The avatars looked to the left or right side of the table and then, after 500ms, items – a bowl, plate, teapot and cup - were presented in either the looked at (valid) or looked away from (invalid) location for 500ms. Participants (n = 50) were told that the cue was not informative and that they were required to remember both the objects' locations and specific details about each object's status, e.g., the bowl could be full or empty. After a 1000ms maintenance interval the participants were presented with a single object in a location on the table and had to respond with whether the object had been in this location originally. They then had to answer a question about the status of an object, e.g. was the bowl empty? We also presented the task using a non-social control cue, specifically a moving stick (within subjects), to help understand whether any influence of the person cue was social, or a basic attention cuing effect. EEG was recorded to measure cortical oscillations in the alpha and theta band during item encoding, maintenance and retrieval. Behavioural results analysed using repeated measure AVOVA show that participants were more accurate for the status question when objects were validly cued by both the social gaze cue and the non-social stick cue. EEG results analysed using cluster-based permutations are used to understand the neural mechanism of this finding, with the social avatar uniquely influencing theta-band brain oscillations, indicating that there is something unique about the social cues influence on cognition.

DISSOCIATION BETWEEN OBJECTIVE AND SUBJECTIVE JUDGMENTS IN UNCERTAIN ENVIRONMENTS

Unique Code: TP001168

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Topic: Cognition and behaviour

Introduction: Choice (Type 1) and confidence judgment (Type 2) about the belief that it is correct usually incorporate sensory uncertainty such that both performance and confidence increase as the uncertainty decreases. However, in some cases confidence and accuracy can dissociate. This suggests that objective and subjective ratings may use different information, or integrate the same information differently. In this pre-registered study, we investigated whether and how environmental uncertainty (changes in stimulus probabilities over time) influences Type 1 and Type 2 judgments. Methods: 52 participants performed a motion discrimination task. We manipulated expectation by having trial periods where either leftward or rightward motion was more likely. We manipulated environmental uncertainty by changing the length of those trial periods: the more probable motion direction changed either frequently (every 50 trials) or infrequently (every 100 trials). Participants completed 600 trials per environmental condition: 12 direction changes (6

for each direction) every 50 trials for the highly uncertain environment and 6 direction changes (3 for each direction) every 100 trials for the less uncertain environment. Approach for statistical analyses: Type 1 judgment: bias to respond "right"; Type 2 judgment: confidence and metacognition (Meta-d'/d'); Speed and extent of the learning of the probabilities: cross-correlation between P(stimulus is right) and: (1) bias to respond "right", (2) confidence for congruent trials, (3) confidence for incongruent trials. Results and conclusions: As we predicted, participants' responses were more biased by expectations in more stable environments. We found that confidence was higher when the response was congruent with the expectation, and that metacognitive sensitivity was higher when the response was incongruent with the expectation. These effects did not increase in a more stable environment. The cross-correlation analysis revealed that only response bias incorporated prior probabilities to a greater extent in a more stable environment. In conclusion, the fact that Type 1 but not Type 2 judgments are influenced by volatility suggests that they do not use the same information, or that they use the same information differently.

Memory for Spatial and Non-Spatial Associations in Developmental Amnesia

Unique Code: TP001194

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Topic: Cognition and behaviour

Patients with developmental amnesia (DA) have been exposed to hypoxic ischemic episodes in early life and have suffered bilateral damage to the hippocampus. These patients have deficits in spatial memory, episodic memory, and recall, but have well-developed recognition memory and semantic memory. According to the Relational Theory of hippocampal function the spatial and memory deficits in DA can result from failure to form relations between items and their contexts. Spatial memory deficits emerge because navigation depends heavily on relational processing. However, given that hippocampal subregions show differential sensitivity to hypoxic injury, it is possible that the pattern of functional deficits in DA is not solely determined by relational binding. In this study, associative memory for spatial versus non-spatial stimuli was investigated. Nineteen patients with DA, 22 typically-developing controls and 11 patients with "moderate" hippocampal damage completed a virtual navigation task. Participants followed a path to visit 8 locations in which they met a virtual person, and received a virtual object at each location. At test, participants were asked to recognise (from a list of foils) the object that was associated with each person (non-spatial association) and the object that was associated with each place (spatial association). A cross-over interaction was observed where typically-developing controls found the non-spatial associations more challenging than the spatial associations, but the reverse was found for the patients with DA. The data are consistent with the notion that while patients with DA have a core deficit in relational memory, they have a particular difficulty with learning spatial associations which cannot be explained by a relational deficit alone.

Combined lateral entorhinal-perirhinal cortex lesions impair multimodal associative recognition memory

Unique Code: TP001197

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Topic: Cognition and behaviour

Lateral entorhinal cortex (LEC) has been hypothesised to process non-spatial, item information that is combined with spatial information from medial entorhinal cortex to form episodic memories within the hippocampus. Recent studies, however, have demonstrated that LEC has a role in integrating features of episodic memory prior to the hippocampus. While the precise role of LEC is still unclear, anatomical studies show that LEC is ideally placed to be a hub integrating multisensory information. The current study tests whether the role of LEC in integrating information extends to long term multimodal item-context associations. A group of 21 rats was trained on a context dependent odour discrimination task where rewards were buried in pots filled with scented sand in two different contexts which served as a cue to the correct odour. Following training, 12 rats were administered bilateral excitotoxic LEC lesions and 9 rats received sham lesions. Rats were then tested on the previously learned odour-context association task. The data were analysed using a mixed factorial ANOVA with group as the between-subjects factor (LEC and Sham lesion) and surgery (pre- and post) as the within-subjects factor. Control rats showed good memory for the previously learned association but rats with LEC lesions were significantly impaired relative to both their own pre-surgery performance and control rats. A separate group of 14 rats was trained on odour and context discrimination tasks alone where rewards were buried in pots of sand with a particular odour or in a particular visual context. Following training, 7 rats were administered bilateral excitotoxic LEC lesions and 7 rats received sham lesions. Across both tasks, there was no difference in the performance of rats with LEC lesions and controls or in their performance before and after surgery. Lesioned rats in both experiments, however, had significant damage to both LEC and the neighbouring perirhinal cortex (PRC). Therefore, the current study demonstrates that LEC-PRC lesions impair multimodal associative but not unimodal recognition memory.

Spatial selective attention and asynchrony of cognitive systems in adult dyslexic readers: An ERPs and behavioral study

Unique Code: TP001205
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Introduction: Previous studies (Breznitz, 2002, 2003) suggest that an asynchrony between the speed of processing (SOP) of the visual (orthographic) and the auditory (phonological) modalities may lead to the word-decoding difficulties observed in dyslexic readers. The aim of the reported study was to explore the associations between the asynchrony phenomenon and spatial selective attention functions in adult dyslexic readers.

Methods: Adults with developmental dyslexia and non-impaired readers underwent two experimental tasks, one including alphabetic stimuli (pre-lexical consonant-vowel syllables) and the other containing non-alphabetic stimuli (pictures and sounds of animals). Participants were instructed to attend to the right or left hemifields and to respond to all stimuli on that hemifield. Behavioral and event-related potential parameters were collected.

Approach for statistical analyses: Several 2 × 2 × 2 repeated measures ANOVA tests were carried out, with attentional manipulation, task, and group, in order to investigate within and between group differences. In addition, time gaps were

calculated in order to investigate if asynchrony exists between the auditory and visual modalities.

Results and conclusions: The main finding of the present study was that the dyslexic readers demonstrated asynchrony between the auditory and visual modalities when alphabetic stimuli were presented to the right hemifield. The findings also suggest that intact reading is dependent on synchronized auditory and visual SOP when spatial selective attention is manipulated. The findings of the current study are discussed in terms of asynchrony between modalities as a neurocognitive marker in developmental dyslexia.

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Effects of the dopamine D2 receptor antagonist Haloperidol on mentalizing performance in healthy adults

Unique Code: TP001214

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Topic: Cognition and behaviour

Background:

Although Parkinson’s disease (PD) is commonly thought of as a “motor disorder”, a burgeoning literature has associated PD with socio-cognitive difficulties. These difficulties could stem from a change in the way interaction partners respond to PD patients. However, socio-cognitive changes may also be related to dopamine system dysfunction. To date, few studies have investigated dopaminergic modulation of social cognition.

Methods:

We used a double-blind, placebo-controlled procedure to test the effect of the D2 antagonist Haloperidol on mental state attribution and motor function, using an adaption of the Heider & Simmel animations task. On two separate days, once after receiving 2.5mg Haloperidol and once after receiving placebo, 33 healthy adult participants first animated two triangles on a touch screen device to depict two mental state- and two non-mental state words. Subsequently, participants viewed and rated an independent set of 32 mental- and non-mental state animations. In addition, drug effects on motor performance were tested using a shapes drawing task. Baseline working memory (WM) was assessed as a proxy for individual baseline dopamine levels.

Bayesian mixed effects models were employed to assess potential main effects of drug (placebo, Haloperidol) on mentalizing accuracy scores and motor function, as well as possible interactions between drug and video type (mental-, non-mental state), and drug and WM score.

Results and Conclusion:

We observed that Haloperidol lowered mental state attribution accuracy for both mental- and non-mental state animations, furthermore Haloperidol resulted in a slowing of drawing movements in participants with low, but not high

WM. We conclude that antagonizing dopamine affected mentalizing accuracy independent of motor function, in that drug effects on movement were mediated by baseline dopamine levels while drug effects on mentalizing were not. We discuss the results in the context of dissociated dopaminergic pathways involved in social cognition and motor control and implications for disorders such as PD.

Effects of dopamine D2 receptor antagonist Haloperidol on movement speed in a drawing task

Unique Code: TP001215

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Topic: Cognition and behaviour

Background:

Decreased brain dopamine has been related to slowed movement response initiation[1] and reduced movement vigour when reaching to a target[2], whilst withdrawal of dopaminergic medication in patients with Parkinson's Disease (PD) leads to disturbed handwriting kinematics[3]. To date, few studies have investigated dopaminergic modulation of movement speed in tasks devoid of the reward-based motivation to move. Moreover, it is important to control for baseline working memory (WM), as research has demonstrated its tight association with baseline striatal dopamine[4].

Methods:

We used a double-blind, placebo-controlled procedure to test the effect of the D2 antagonist Haloperidol on movement speed during a simple drawing task. On two separate days, once after receiving 2.5mg Haloperidol and once after receiving placebo, 41 healthy adult participants used a stylus to draw a range of shapes on a Wacom touchscreen. X and y position was recorded at 133Hz. For each participant indices of overall speed were derived.

Results and Conclusion:

A linear mixed effect model examined the impact of drug on drawing speed as a function of shape and baseline dopamine levels (indexed by baseline WM). Drawing speed differed as a function of shape and following administration of Haloperidol, participants' drawing speed was significantly slowed compared to placebo. Crucially, there was an interaction between drug and baseline WM performance, such that those with low baseline WM (i.e low baseline dopamine) showed greater slowing in drawing speed following Haloperidol than those with high baseline WM (Fig. 1). Our results support the role of dopamine in drawing speed and advocate the use of the current task to assess movement atypicalities in PD.

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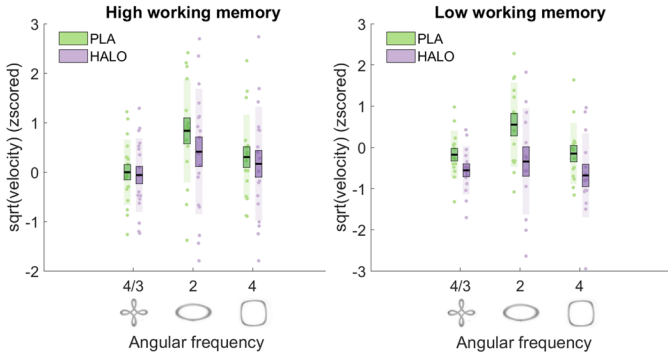

EEG Neurofeedback has a small but positive effect on memory performance: A meta-analysis of controlled studies in healthy volunteers

Unique Code: TP001216

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Topic: Cognition and behaviour

Introduction: Electroencephalography Neurofeedback (EEG-NF) is a self-regulatory technique where an individual receives real-time feedback on a pattern of brain activity that is theoretically linked to a target behaviour. Several studies have examined whether EEG-NF can enhance memory performance but have generated mixed results. Furthermore, it is currently difficult to draw strong conclusions owing to inconsistencies in EEG-NF procedures, reporting of results and inadequate design features, such as a lack of control condition. Therefore, the aim of this research was to conduct a meta-analysis of appropriately designed studies to determine whether EEG-NF can enhance memory.

Methods: A literature search was conducted using key search terms. This returned 40 studies, with 22 meeting the inclusion criteria. The relevant data were extracted to calculate an effect size for each outcome within a study. Appropriate corrections were applied to account for differences in study design and sample size.

Approach for statistical analysis: A meta-analysis was conducted in R using robust variance estimation (RVE) to account for multiple effect size estimates within each study. A combined effect size was generated to summarise the overall effect of EEG-NF on memory performance. Moderator and sub-group analyses were performed on the data to investigate whether effect size was influenced by factors such as EEG-NF protocol, training schedule, electrode site, memory type, control group, timing of the memory task, and age.

Results and conclusions: Twenty-two studies were included in the final analysis, which produced a total of 55 effect sizes from 536 participants' data. There was a small but significant positive effect of EEG-NF on memory performance ($g = 0.31$), with a relatively low level of heterogeneity ($I^2 = 27.6\%$, $\tau^2 = 0.07$). No significant moderators of the combined effect size were revealed. Thus EEG-NF significantly enhances memory performance relative to an active control condition in healthy adults. This offers the potential that EEG-NF training could be applied to populations with memory decline, such as older adults.

A cortical model for reversal learning without a reward prediction error but Hebbian learning and serotonin controlling its plasticity

Unique Code: TP001223
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Topic: Cognition and behaviour

Introduction

Theoretical models of reversal learning usually use the dopaminergic reward prediction error generated in the sub-cortical structures. However, it has long been argued (Rolls, 2008) that the reward related behavioural flexibility is rather cortical than sub-cortical and not dopamine driven.

Methods

A computer simulated rat has to find food at one of two landmarks and then after successful learning the food is moved to the other landmark. Instead of a reward prediction error, learning of the stimulus/reward associations is Hebbian LTP by feeding the primary reward postsynaptically into the orbitofrontal cortex (OFC) while place and landmark information is its pre-synaptic activity. LTD is triggered when the primary reward is not driving the OFC causing less and slower changing postsynaptic activity. The same plasticity rule is used downstream in the mPFC selecting the actions (see Panel B). Serotonin acts as an accelerator for both LTP and LTD. Experiments were run for a control scenario, for one with less serotonin and one with a simulated application of serotonin reuptake inhibitors.

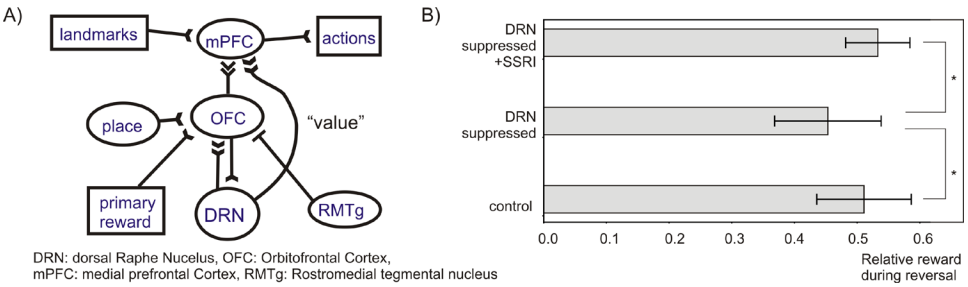
Approach for statistical analysis

Every experiment ran 30 times and during reversal the relative reward was calculated which is the number of successful food retrievals against any attempts to go to either landmark. A t-test was applied at $p = 0.05$.

Results and conclusions

We show that Hebbian learning is able to model reversal learning (Panel B, control) and that serotonin acts as an accelerator of flexibility. Reduced serotonin increases the number of non-rewarding actions during reversal (Panel B, DRN suppressed). SSRIs can help to overcome this deficiency (Panel C, DRN suppressed + SSRI) but we'd predict that any drug boosting plasticity will have this effect. Crucial is that as shown in our previous study (Porr et al 2019) this boosts the average rewards which in turn influences motivation & mood.

Rolls, E. T., Grabenhorst, F (2008) The orbitofrontal cortex and beyond: From affect to decision-making. Progress in Neurobiology.
Porr, B & Miller, A & Trew, A (2019) An investigation into serotonergic and environmental interventions against depression in a simulated delayed reward paradigm. Adaptive Behaviour.



DRN: dorsal Raphe Nucelus, OFC: Orbitofrontal Cortex, mPFC: medial prefrontal Cortex, RMTg: Rostromedial tegmental nucleus

Brain stimulation of right dorso-lateral prefrontal cortex increases cognitive reflection performance

Unique Code: TP001249

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Topic: Cognition and behaviour

Decision-making engages a network of neural regions which include the dorsolateral prefrontal (DLPFC) and orbitofrontal cortices (Hare, Camerer, & Rangel, 2009). TDCS is a non-invasive neurostimulation technique that uses low direct current intensities to modulate cortical excitability in a targeted region. However, so far effects of tDCS on judgment or decision-making tasks have not been reliable in contrast to a sham stimulation.

We investigated whether judgment/decision performance is modulated by anodal stimulation to the (right) DLPFC. TDCS was delivered via a battery-driven stimulator with two sponge electrodes (1.5 mA). Stimulation lasted for 20 minutes (with no task). A second block with judgment tasks was completed after stimulation ended.

Participants were randomly allocated to the following tDCS montages: 1. anode right DLPFC/return left DLPFC, 2. anode left DLPFC/return right DLPFC or 3. sham condition (no stimulation).

We used three tasks: 1. The cognitive reflection test (CRT) is a measure of cognitive reflection ability (11 CRT items). 2. Ten vignettes measuring susceptibility to using the representativeness heuristic were given to participants (n=54; mean age = 24.6; 29 females). 3. Eight logic syllogism tasks were also given. Potential individual differences of thinking dispositions and general cognitive ability (cognitive characteristics) were also measured.

(M)ANOVAs showed a significant effect of stimulation on CRT scores after right DLPFC anodal stimulation in comparison to both left DLPFC stimulation and sham. A similar pattern was observed for representativeness (heuristic) vignettes correct answers, but not for logic scores. Cognitive characteristics showed no effect of stimulation group ($p = .28$). A second experiment with 48 participants (mean age = 26.08; 21 males) confirmed this pattern, and also showed that repeated (2 sessions) stimulation still increased CRT scores.

These experiments provide evidence that neuromodulation of the right DLPFC affects judgment and decision-making. Increasing cortical excitability in the right DLPFC boosts reflective (analytic) thinking performance, when controlling for individual cognitive differences.

Hippocampal disinhibition reduces cue and contextual fear conditioning whilst sparing the acquisition of latent inhibition at pre-exposure

Unique Code: TP001253

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Topic: Cognition and behaviour

Hippocampal neural disinhibition (reduced GABAergic inhibition) is a key feature of schizophrenia pathophysiology (Heckers & Konradi,2015,SchizophrRes). The hippocampus is part of the fear circuit and can modulate prefrontal and

striatal mechanisms, including dopamine signalling (Bast et al,2011,CurrOpinNeurobiol), which play a role in salience processing (Lingawi et al,2018,NeurobiolLearnMem; Morrens et al,2020,Neuron). Therefore, hippocampal neural disinhibition may contribute to impairments in fear conditioning and salience modulation associated with schizophrenia (Jensen et al,2008,Neuropsychopharmacology).

To test this hypothesis, we examined the effect of ventral hippocampal disinhibition by picrotoxin (GABA-A antagonist) infusion in rats (McGarrity et al,2017,CerebCortex) on fear conditioning and salience modulation, as reflected by latent inhibition (LI), using a conditioned-emotional response paradigm with a visual conditioned stimulus (CS, a flashing light) (Nelson et al,2011,JPsychopharm). Reduced conditioning in rats pre-exposed (PE) to the CS, compared to rats non-pre-exposed (NPE) to the CS, was used to measure LI. Picrotoxin or saline were infused prior to both pre-exposure and conditioning (Exp.1) or pre-exposure only (Exp.2). Data were analysed by ANOVA with infusion and pre-exposure as between-subjects factors.

In Exp.1, hippocampal disinhibition virtually abolished fear conditioning to the CS, as reflected by markedly reduced conditioning in picrotoxin compared to saline rats in the NPE group; this resulted in similarly low conditioning in PE and NPE picrotoxin rats, whereas saline rats showed marked LI, as reflected by stronger conditioning in PE than NPE rats (Fig.1A). Hippocampal picrotoxin prior to pre-exposure and conditioning also reduced contextual fear conditioning during re-exposure to the conditioning context (not shown). In Exp.2, hippocampal picrotoxin at pre-exposure only did not affect the acquisition of fear conditioning or LI (Fig.1B).

Overall, ventral hippocampal disinhibition markedly disrupted fear conditioning to a visual CS, which resembles reduced aversive conditioning in schizophrenia. However, we found no evidence that hippocampal disinhibition disrupts the acquisition of latent inhibition.

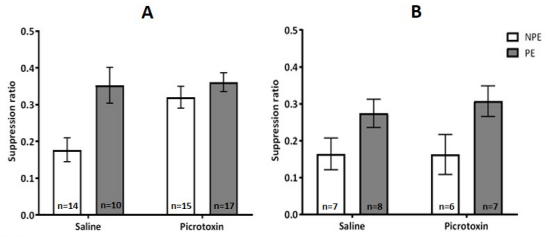

Figure 1. Conditioning to the light CS as reflected by mean suppression ratio (±SEM) for non-pre-exposed (NPE: white bars) and pre-exposed (PE: grey bars) groups after ventral hippocampal saline or picrotoxin (150ng/0.5µl/side) infusion (numbers in the bars indicate number of rats per group). Suppression ratio calculated as A/(A+B), with (A) the time to 50 licks prior to CS and (B) time taken to 50 licks after onset of CS. Note: the lower the mean suppression ratio the stronger conditioning to the CS. **A**: Exp.1 - Effect of ventral hippocampal infusion of saline or picrotoxin at pre-exposure and conditioning. Fear conditioning to the CS is virtually abolished by hippocampal disinhibition, as reflected by higher suppression ratio in picrotoxin-infused compared to saline-infused rats in the NPE group (white bars). In saline rats, there was marked LI, as reflected by lower conditioning (higher suppression ratios) in the PE compared to NPE group; this was not apparent in picrotoxin rats, where both PE and NPE groups showed virtually no conditioning (high suppression ratios). **B**: Exp. 2 - Effect of ventral hippocampal infusion of saline or picrotoxin at pre-exposure only. Pre-exposure reduced fear responding to the CS (high suppression ratios) in both saline and picrotoxin infused rats, reflecting intact LI.

Exploring Striatal Function Using The Gap Crossing Test on The zQ175 Mouse Model of Huntington's Disease

Unique Code: TP001278
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Topic: Cognition and behaviour

Introduction:
Huntington's Disease (HD) is a fatal neurodegenerative disorder which presents with a combination of locomotor, psychiatric and cognitive symptoms. The primary pathology associated with HD occurs in the striatum in humans and this is replicated in many of the HD mouse models for study. The striatum is associated with locomotion, decision making & goal orienting behaviour in mice and humans. In HD, disruption to dopaminergic transmission and degeneration of neurons in striatum is thought to lead to deficits in these behaviours.

Methods:
This project used the gap-crossing test to look at decision making and goal-directed behaviour in the zQ175+/- HD mouse & wild-type littermates. This test is used to study whisking behaviour but we implemented it in a novel way to examine whether early deficits in decision-making behaviour could be detected in zQ175+/- mice.

Mice were habituated to the test apparatus and were motivated to traverse the track and cross the gap by the goal of the home cage at the end of the track. Mice were trained with no gap in the track, then exposed to a randomised sequence of gap widths with an overhead camera recording their position. AnyMaze (Stoelting) was used to calculate speed and latency to cross the gap and an observer recorded whether or not a successful crossing was made. Mice were also observed in the open field apparatus to check for any signs of overt locomotor impairment.

Approach for statistical analysis:
A two-way ANOVA was performed for each measured parameter at individual gap widths that the genotypic groups performed. If results proved significant; a Tukey post hoc test was then applied.

Results & Discussion:
An open-field test highlighted that no locomotor deficits were seen in the HD mice. There was a significant difference between change of gap width at each measurement. There was no significant difference between genotype at any decision-making measurement. The HD mice could not perform the 9cm gap cross when compared to WT. The gap crossing test could not distinguish differences in decision-making behaviours between HD & WT mice. A power analysis showed that 15 mice per genotype is required to demonstrate a significant difference between genotypes in latency to gap cross.

Shared structure between simple 2D conceptual spaces accelerates learning

Unique Code: TP001279
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Topic: Cognition and behaviour

Recent experimental and theoretical work has supported geometric theories of conceptual representation, where concepts are defined as regions in an abstract n-dimensional space with each dimension specifying a certain characteristic. A key question in cognitive neuroscience concerns the generalisation of information between such concepts, when existing domains of conceptual knowledge accelerate learning of incoming congruent information. In order to understand this phenomenon, an experimental paradigm is needed that would allow careful and systematic manipulation of stimuli and task characteristics and examination of their influence on generalisation.

We developed an online paradigm for capturing generalisation of knowledge between simple 2-dimensional concepts. Participants successively learned two new concepts: birds defined by the size of their neck and legs and birds defined by the size of their beak and tail. Through a rote trial-and-error procedure, the participants learned that specific exemplars of each concept were associated with arbitrary target stimuli which served as “landmarks” in the corresponding 2D conceptual spaces. Crucially, for one group of participants (congruent) the geometry of the arrangement of paired-associates was identical between the two bird-spaces, whereas for another (incongruent) it was maximally different. We predicted that in the congruent group, the paired-associates learning for the second bird-space would be accelerated thanks to generalisation of knowledge of their arrangement in the first bird-space.

We preregistered a Bayesian sequential analysis to examine relative support for the null and the alternative hypotheses, setting the respective Bayes Factor thresholds BF01 and BF10 to six. We found strong evidence in support of H1 that acceleration of learning was faster in the congruent than in the incongruent group, demonstrating the validity of this paradigm for capturing generalisation of knowledge across conceptual spaces. In future experiments, we plan to examine various modulatory factors on generalisation, such as types of dimensions defining the 2D spaces (quantitative vs qualitative), the geometry of arrangement of target toys and the learning method for the paired-associates.

The involvement of CREB transcription factors and global protein expression in memory consolidation in Lymnaea stagnalis

Unique Code: TP001284

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Topic: Cognition and behaviour

Introduction: The process of transcription, including CREB signalling, is important in memory consolidation across species. CREB2 is known to act as a memory repressor via inhibiting CREB1-initiated gene transcription but data is lacking about the timing of changes in mRNA and protein expression of CREB1 and CREB2 during the consolidation process. Our finding that memory lapses occur at 30 min and 2 h after single-trial conditioning in Lymnaea (1,2), opened the way for us to study these changes. We tested the hypothesis that CREB1 and CREB2 mRNA and protein expression levels differ in lapse and non-lapse periods during memory consolidation.

Aims: To establish differences in CREB mRNA and protein expression during phases of memory consolidation after single trial associative conditioning.

Methods: Brains were extracted from conditioned and naïve animals at the two memory lapse time points and in a non-lapse period of consolidation (1 h post-training) and processed for qRT-PCR, Western blotting and LC-MS based proteomics.

Approaches to Statistical Analysis: Statistical comparisons were made with Kruskal-Wallis one-way ANOVA analysis or Unpaired Student’s t-test with Welch’ correction.

Results: CREB2 mRNA expression was downregulated in both periods of memory lapse without affecting CREB1 mRNA

expression, thus the ratio of CREB1/CREB2 mRNA significantly increased in both memory lapse periods. Phosphorylation of CREB1 and CREB2 protein expression significantly decreased at the 2-hour lapse, without affecting CREB1. During the lapse and non-lapse periods, we found differentially expressed proteins involved in histone modifications, transcription, translation and kinases involved in the activation of CREB signalling.

Conclusions: During the lapse periods there are changes in the process of transcription and histone modifications that could play key roles in the transition between different stages of memory consolidation. We show a differential role for CREB2 at the two lapse time points, but further experiments are needed to determine the interaction of CREB1 and CREB2 during other stages of memory consolidation.

1. Marra et al. (2013) Nat Commun:4:1578.
2. Crossley et al. (2019) Commun Biol:2:242.

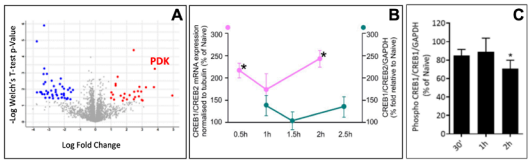

Figure 1: The effects of single-trial food reward classical conditioning on global protein expression and CREB transcription factors in the 'learning ganglia' of *Lymnaea stagnalis*. A. Volcano Plot of protein expression in a lapse (2h) and a non-lapse period (1h). Coloured spots indicate differentially expressed proteins (Blue: Down-regulated proteins; Red: Upregulated proteins). PDK (Phosphoinositide-dependent kinase) is a Serine/threonine kinase, known to be involved in CREB signalling. **B.** RT-qPCR and WB experiments show time-dependent changes in the ratios of CREB1 and CREB2 mRNA and protein levels. The ratio of CREB1/CREB2 mRNA (pink dots) is significantly higher at the 30 min and 2 h memory lapse points, but not at the 1 h non-lapse time point, compared to the naïve baseline (100). The corresponding protein ratios (green dots) follow the same trend as the mRNA ratios but with a 30 min delay. **C**. Phosphorylation of CREB1 is significantly decreased at the 2-hour lapse period, compared to the naïve level (100%). Results are expressed as mean ± SEM of 5-6 separate experiments. *P<0.05 by unpaired t-test with Welch's correction.

Contextual vs. probabilistic learning of target-scene associations differentially support retrieval and attentional orienting

Unique Code: TP001305

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Topic: Cognition and behaviour

During visual search we quickly learn to orient towards an object's probable location, which enables us to efficiently sort through clutter from the visual world to find our target. Research has established that this process is facilitated when learning of target locations is based on hippocampal-dependent spatial contextual associations (CC, contextual cueing) or striatal-based probabilistic regularities (LPL, location probability learning). Here, we tested how these different types of learning aid the future use of established memories. In two online experiments, participants searched for targets within scenes. Depending on the scene category, the target consistently appeared at a specific location (CC), within a hemifield (LPL), or was unpredictable (random). After learning the target-scene associations, in Experiment 1, 54 participants were tested on their memory for both the hemifield and the specific location of the learned targets. Participants showed enhanced recall performance for target hemifield and specific target location in both LPL and CC

conditions. However, when learning performance was low (low accuracy/high reaction time), LPL facilitated memory for target hemifields, and when learning performance was high, CC facilitated memory for specific target locations. In Experiment 2, after the learning phase, 54 participants were tested on their ability to orient attention to targets flashed either in a learned specific location or hemifield. We found greater orienting benefits, i.e. reduced reaction times, for CC compared to LPL. In both experiments, planned paired-samples T-tests and ANOVAs were conducted to examine the effect of learning type on speed and accuracy of memory recall and attentional orienting. Together, our results provide evidence that contextual and probabilistic learning systems give utility for future retrieval of learned associations, but the way in which these systems promote memory retrieval may be related to the quality of encoding. Further, attentional orienting appears to be more profoundly guided by contextual, compared to probabilistic regularities, regardless of learning quality. Our work paves the way for a more nuanced view of how these memory systems cooperate and/or compete to guide adaptive behavior within a single experimental framework.

Investigating hippocampus-midbrain functional connectivity during consolidation in the context of reward and curiosity-motivated learning

Unique Code: TP001307

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Topic: Cognition and behaviour

Human memory is selective and not all experiences are encoded. Both, reward and curiosity have been found to facilitate encoding by dopaminergic midbrain (VTASN) projections to the hippocampus (HPC). While reward-motivated learning (RML) effects only occur after long delays (Murayama & Kuhbander, 2011), curiosity-motivated learning (CML) effects can be found after short and long delays (Stare et al., 2018) suggesting that RML & CML rely on different post-encoding (PE) mechanisms. We examined the relationship between RML, CML, and consolidation supported by dopamine (consoliDopa; i.e. PE functional connectivity (FC) between HPC and VTASN) to investigate whether RML influences consoliDopa and its relationship with encoding success and the curiosity-driven memory enhancement (CMLE).

Participants watched 36 magic tricks inside the MRI scanner and rated their curiosity (incidental encoding; memory tested after one week). In the reward group (n=25), participants could earn additional monetary rewards by correctly answering a question whereas such rewards were not provided in the control group (n = 25). Resting state data was acquired pre- and post-learning.

Pearson correlation was used to quantify pre- and post-learning FC between HPC and VTASN and consoliDopa (i.e. change in HPC-VTASN FC from pre to post) was correlated with behavioural measures of learning. In the absence of a reward effect on consoliDopa ($t(47.68) = .253$, $p = .802$), there were reward effects on how consoliDopa predicts encoding and CMLE. While there was no correlation between consoliDopa and encoding ($r = -.23$, $p = .278$) or CMLE ($r = .15$, $p = .476$) in the control group, consoliDopa significantly predicted encoding positively ($r = .51$, $p = .008$) and CMLE negatively ($r = -.53$, $p = .007$) in the reward group. The difference in correlation was significant (encoding diff = -.74, $p = .008$; CMLE diff = .67, $p = .014$).

Our results show that only in the context of RML consoliDopa supports encoding and that consoliDopa decreases as the CMLE increases. Taken together with the absence of any predictive effects of consoliDopa in the control group, this

suggest CML might be less reliant on consoliDopa than RML. Hence, future research is needed to better understand the networks supporting CML.

Human electroencephalographic correlates of defensive approach towards a social threat.

Unique Code: TP001317

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Topic: Cognition and behaviour

Introduction:
The behavioural inhibition system (BIS) is thought to respond to goal conflict and motivate defensive approach towards threats (1). There is substantial neurological evidence for this theory in non-human animals (1). Conversely, in humans, there is growing neurological evidence that the BIS responds to goal conflict (1-2) and almost no neurological evidence that it motivates defensive approach. To address this, we used a social stimulus to create threat within a goal conflict task and recorded electroencephalogram (EEG) activity.

Methods:
Participants repeatedly 'approached' a confederate in a dark room by making eye contact. The confederate's distance and expression varied between trials to adjust the threat level and the participant's motivation for defensive approach. Continuous EEG activity was recorded and transformed into current source density (CSD) power and coherence spectra within the theta and alpha wavebands.

Approach for statistical analysis:
EEG data were entered into a PCA to produce spatial components. EEG data within the spatial components were then compared between high and low defensive approach conditions using hierarchical ANOVAs. Forced entry regression models were used to identify any EEG variables that predicted psychometric scores.

Results and conclusions:
Theta coherence significantly increased and alpha CSD power significantly decreased during the high defensive approach condition. The increased theta coherence provides evidence that the BIS does direct defensive approach in humans, as previously found in animals.The decreased alpha CSD power suggests that the stimuli were highly engaging. Subsequently, social stimuli should be considered for use in future goal conflict experiments.

References:
1. McNaughton, N., & Corr, P. J. (2014). Approach, avoidance, and their conflict: the problem of anchoring. Frontiers in Systems Neuroscience, 8, 124. https://doi.org/10.3389/fnsys.2014.00124

2. Lockhart T. S., Moore R. A., Bard K. A., and Stafford L. D. (2019) Increases in theta CSD power and coherence during a calibrated stop-signal task: implications for goal-conflict processing and the Behavioural Inhibition System. Personality Neuroscience. Vol 2: e10, 1–14. https://doi.org/10.1017/pen.2019.

Activation of Person Knowledge in Medial Prefrontal Cortex during the Encoding of New Lifelike Events

Unique Code: TP001331

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Topic: Cognition and behaviour

Introduction: Our knowledge about people can help us predict how they will behave in particular situations and interpret their actions. In this study, we investigated the cognitive and neural effects of prior person knowledge on the encoding and retrieval of novel life-like events.

Methods: Healthy human participants learnt about two characters over a week by watching 6 episodes of one of two situation comedies, which were both centered on a young couple. In the scanner, they watched and then silently recalled 20 new scenes from both shows that were all set in unfamiliar locations: 10 from their trained show and 10 from the untrained show. Outside the scanner, participants performed a memory test for the videos they saw in the scanner.

Approach for statistical analysis: Using a logistic mixed-effect model we found that participants' memory was better for scenes from the trained show when compared to the untrained show. We used representational similarity analysis combined with t-tests to examine the functional magnetic resonance imaging (fMRI) patterns of brain activity.

Results and Conclusions: We found that brain activity patterns when watching the videos were reinstated during recall, but this effect was not modulated by training. However, person knowledge boosted the similarity in fMRI patterns of activity in the medial prefrontal cortex (MPFC) when watching the new events involving familiar characters. Higher brain pattern similarity across the trained clips predicted better memory performance. Our findings identify a role for the MPFC in the representation of schematic person knowledge during the encoding of novel, lifelike events.

Investigation of the Effect of Subclinical Autistic Traits on Theory of Mind and Empathy Skills in Healthy People

Unique Code: TP001348

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Topic: Cognition and behaviour

Introduction: It is known that Theory of Mind (ToM) and empathy skills, which defining as the ability to understand others' intentions, wishes, and emotions, are impaired in Autism Spectrum Disorder (ASD). It has been suggested that impairment in ToM and empathy can also be evident in people with Broad Autism Phenotype (BAP). However, studies often focused on individuals, including first-degree relatives of people with ASD, thus there is no consensus on the social-cognitive skills of healthy individuals with autistic behavior tendencies. Accordingly, this study aimed to examine the relationship between subclinical autistic traits and ToM and affective - cognitive empathy skills in healthy individuals.

Methods: 349 (212 female – 137 male) healthy adults ranged 18- 35 years were included in this study. Whereas Autism-Spectrum Quotient (AQ) was used to measure subclinical autistic traits, socio–cognitive abilities were assessed by using Interpersonal Reactivity Index (IRI) and Reading the Mind in the Eyes Test (RMET).

Approach for statistical analysis: The data analysed using SPSS 27.0. Independent sample t-test was used to compare empathy and ToM scores between groups. Pearson correlation analysis and linear regression were performed to examine the relationships.

Results and conclusions: The results showed that women performed better on cognitive and affective IRI, and RMET. According to the regression analysis, while the communication subscale of the AQ predicted the performance of RMET, other subscales of AQ, attention switching and imagination, were predictors of IRI scores. These results suggest that subthreshold autistic traits may have a negative effect on socio-cognitive abilities, such as mentalizing and empathy.

Overlap between cues and targeted memories brings the pre-retrieval control of recollection: two ERP studies on selective remembering

Unique Code: TP001351

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Topic: Cognition and behaviour

Introduction

The ability to select relevant information from memory allows us to draw effectively on our past experiences. But this pre-retrieval selection of recollection is not always possible. We contrasted two candidate mechanisms: that the targeted information is easy to recollect, or that retrieval cues overlap with targeted memory traces. In two encephalographic event-related potential (EEG/ERP) experiments we tested whether stronger cue-target overlap would enable selective recollection even when memory was better for non-targeted items. We quantified selective recollection of targeted over non-targeted information using the left-parietal old/new effect (an established neural marker of recollection), and assessed goal-related ERPs elicited by new items.

Methods

Participants studied object pictures and auditory object names, then their goal was to target one of these sources in each of two memory tests. We manipulated cue-target overlap by probing memory with visually-presented object names (Experiment 1, N=28) or line drawings (Experiment 2, N=28). We computed ERPs for correctly recognized current targets (hits), and correctly rejected (CRs) non-target studied and new items.

Approach for statistical analysis

All analyses were pre-registered (osf.io/j84z6; osf.io/pqn4z). To test our main hypotheses about selectivity of recollection, we tested for effects of target designation on the left parietal effect for targets and non-targets using focal ANOVAs on data from P1, P3 and P5 electrodes from 500-800ms. Goal-related ERP effects were tested using ANOVA on new item ERPs within a 3x3 grid of frontal, central and parietal electrodes from 300-600ms, 600-900ms, and 900-1200ms.

Results and conclusions

Results revealed that the left-parietal effect was selective for targets when test cues overlapped more with the targeted than non-targeted source, i.e., when auditory words were targets in Experiment 1 and when pictures were targets in Experiment 2 – despite consistently better and faster memory for pictures than auditory words, Fig.1. As expected, goal-

related ERP effects also tracked the degree of cue-target overlap. Together these findings show that cue overlap enables selection prior to recollection, as predicted by the encoding specificity principle.

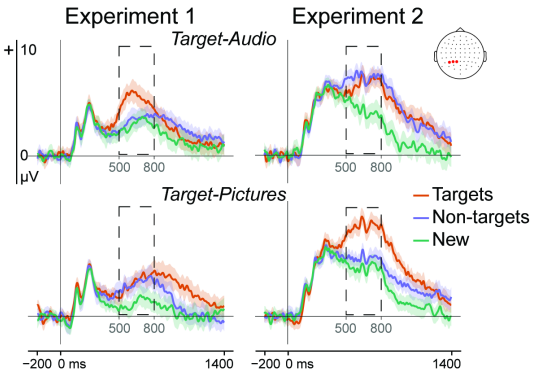

Fig.1. Selectivity of left-parietal old/new effects. Mean grand-average ERP waveforms for target hits, non-target and new CRs over electrode sites (P1, P3, P5), plotted seperately by Target Designation: Experiment 1, with visual word cues, Experiment 2, with pictorial cues. Dashed areas show the analysed time-window. Shaded areas show the adjusted Cosinueau-Morey 95% confidence intervals per time-point.

Mobile EEG reveals the neuro-cognitive processes of real-world obstacles avoidance

Unique Code: TP001367

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Topic: Cognition and behaviour

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Negotiating the environment while walking requires the ability to make fast online motor transformations in response to dynamic changes such as the appearance of unexpected obstacles. The development of mobile EEG technology means it is now possible to monitor the brain in complex real-world environments. Here we used this approach to reveal the neuro-cognitive processes that allow humans to negotiate an obstacle while walking. Participants walked along a path while stepping over expected and unexpected obstacles projected on the floor, allowing us to capture the dynamic oscillatory response to changes in environmental demands. Time-frequency analysis of EEG data identified distinct neural markers, reflecting the different cognitive aspects of obstacle avoidance. Compared to obstacle-free walking, the EEG data revealed clear neural markers of proactive and reactive forms of movement control (occurring before and after crossing an obstacle), visible as increases in frontal theta and centro-parietal beta power respectively. Critically, the temporal profile of changes in frontal theta allowed us to arbitrate between early selection and late adaptation mechanisms of proactive control. Our data show that motor plans are updated as soon as an upcoming obstacle appears, rather than when the obstacle is reached. In addition, regardless of whether motor plans required updating, a clear beta rebound was present after obstacles were crossed, reflecting the resetting of the motor system. Overall,

mobile EEG recorded during real-world walking provides novel insight into the neural basis of dynamic motor control in humans, allowing us to arbitrate between competing theoretical accounts of cognitive control.

Medial prefrontal cortices integrate reward contingencies and structural task knowledge to guide memory generalisations

Unique Code: TP001376

Authors: Sam C Berens - School of Psychology University of Sussex, Chris M Bird - School of Psychology University of Sussex,

Topic: Cognition and behaviour

Introduction

Contemporary models hold that memory generalisations may be achieved in two ways: retrieval-based mechanisms that integrate disparate pieces of information on-the-fly and encoding-based mechanisms that learn generalised task representations during training. Here we hypothesised that two factors may influence the use of each mechanism; whether information is learnt via 'progressive' or ‘interleaved’ training, and whether there has been a period of overnight consolidation.

Methods

34 participants learnt pairwise discriminations between visual features in a reinforcement learning task over 2 consecutive days. The contingencies learnt on each day implied a transitive hierarchy allowing inferences between novel feature combinations. The structure of the training session varied across participants; half encountered discriminations in an order that reflected the underlying transitive hierarchy (progressive training) while the remaining participants encountered discriminations in a random order (interleaved training). During fMRI scanning, participants were tested on well-practised and inferred discriminations from each day of training.

Statistical analyses

We used generalised mixed-effects models to test the influence of ‘training method’ (progressive vs interleaved) and ‘retention interval’ (day 1 vs 2) on transitive inference. Specifically, we explored whether these experimental factors influenced the use of encoding- and retrieval-based mechanisms by testing behavioural and fMRI predictions of each account.

Results and conclusions

Progressive training yielded substantially better generalisation than interleaved training, yet behavioural and fMRI analyses found little evidence that this was driven by the use of different generalisation mechanisms. Instead, we found converging evidence for use of encoding-based mechanisms in all conditions. BOLD similarity analyses implicated the left hippocampus, entorhinal cortex, and medial prefrontal cortex (MPFC) in maintaining a generalised task structure akin to successor representation. However, only representations in the MPFC were modulated by training method. Other than reducing response times, overnight consolidation appeared to have little effect on behavioural indices of generalisation.

Strain differences between albino Wistar and pigmented Lister Hooded rats in inhibitory discrimination learning and novel object recognition tasks

Unique Code: TP001380

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Topic: Cognition and behaviour

Strain differences in visual abilities and exploratory tendencies can confound rats' performance in cognitive tests of learning and memory. In the present study we compared the performance of albino Wistar and pigmented Lister Hooded rats in appetitive conditioning and recognition memory procedures, specifically within-subjects inhibitory learning (A+/AX-) (Rescorla, 1965, Psychol. Bull), and novel object recognition (NOR) variants (Ennaceur & Delacour, 1988, Behav. Brain Res; Dere et al., 2007, Neurosci. Biobehav. Rev). The inhibition task included an excitatory training stage, summation and retardation tests. NOR was tested after a 10 min delay, 24hr delay and using a recency variant. The systematic comparison of the performance of Lister Hooded and Wistar rats in the inhibitory learning and NOR tasks was done with the objective to test the evidence for the presumed superiority of the Lister Hooded strain in such tasks. Data were analysed by analysis of variance in mixed factorial designs with the between-subjects factor of strain (Wistar or Lister Hooded). Planned comparisons were used to determine the presence or absence of behavioural effects for each of the strains (e.g one sampled t-tests on the NOR discrimination ratios). In both experiments, differences in activity were taken into account. In the inhibitory learning procedure, Listers showed more magazine activity prior to stimulus presentations than Wistars. This strain difference was mitigated by the use of difference scores and there was no strain difference in associative learning at the excitatory training stage. Follow up analyses by strain suggested that the Wistars went on to show some performance advantage at the inhibitory discrimination stage and marginally better retardation test performance. In the NOR tasks, both strains performed well in the 10 min delay variant. In the 24hr delay and relative recency NOR variants, there was still no significant effect of strain, but the planned comparisons suggest that the Lister Hooded rats tended to show some performance advantage. Overall the results of the present study confirm the suitability of Wistars for use in associative learning and basic NOR procedures.

Computational and theoretical neuroscience

The effect of sleep quality on global structural connectivity in bipolar disorder

Unique Code: TP001148

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Topic: Computational and theoretical neuroscience

Introduction: Bipolar disorder (BD) is characterized by significant sleep disturbances and changes in the topological organisation of the brain's connectome resulting in reduced communication efficiency and segregated processing abilities. Connectome studies on sleep deprivation found associations between sleep deficiency and aberrant network topology, however, this relation in bipolar disorder remains unknown. We employed a network analysis approach to investigate structural brain alterations underlying sleep deficits in BD.

Methods: Participants with BD (n=36: mean±SD, 42±13) and healthy controls (HC) (n=37, 38±14) underwent T1-weighted and diffusion-weighted MRI (3T Philips Achieva) and sleep assessment (Pittsburgh Sleep Quality Index). For all

participants, 86x86 binary, fractional anisotropy-weighted, and number of streamlines-weighted, undirected connectivity matrices were constructed to derive 14 global connectivity measures.

Approach for statistical analysis: A Mann-Whitney U Test evaluated sleep quality difference between BD and HC groups. A multivariate analysis of covariance examined the effect of sleep quality on 14 measures of structural connectivity in the total sample and investigated an interaction between sleep quality and diagnosis while covarying for PSQI scores, diagnosis, age, and gender.

Results: Sleep quality was significantly lower in individuals with BD in comparison to healthy participants (U=966, p<0.001). This difference was not expressed by altered structural connectivity of the whole-brain network in the total sample (F=0.715, p=0.750), nor in participants with BD relative to HC (F=0.876, p=0.588).

Conclusions: Despite the lower sleep quality in bipolar disorder compared to healthy controls, and widespread aberrant brain topology common within the disorder, sleep deficiency was not reflected in structural changes of the whole-brain network in this population. The absence of group differences suggests that the effect of sleep deficits on the brain structure may be homogenous across populations, rather than be illness-specific, or may involve more local subnetwork changes.

Figure 1. Non-significant associations between sleep quality (PSQI scores) and measures of global topology (fractional anisotropy-weighted global efficiency, characteristic path length, and strength) in bipolar disorder versus healthy controls group.

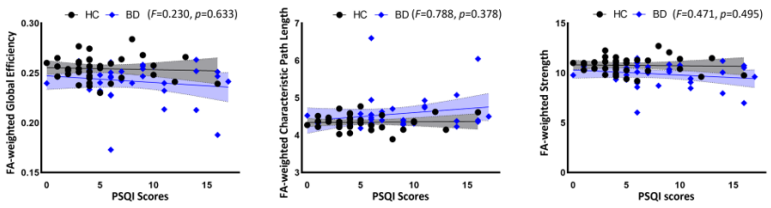

Figure 1 legend: Healthy controls (HC) are represented by black circles, grey regression lines and grey shaded 95% confidence intervals. Individuals with bipolar disorder (BD) are represented by blue diamonds, blue regression lines, and blue shaded 95% confidence intervals.

Bilateral Disconnection of White Matter Tracts Mediates The Incidence of Vestibular Agnosia

Unique Code: TP001202

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Topic: Computational and theoretical neuroscience

Bilateral Disconnection of White Matter Tracts Mediates The Incidence of Vestibular Agnosia

Yuscah Pondeca, Zaeem Hadi, Elena Calzolari, Mariya Chepisheva, Heiko Rust, David J Sharp, Mohammad Mahmud, Barry M Seemungal

Vestibular Agnosia (VA) is a perceptual syndrome characterized by an attenuated vestibular sensation of self-motion despite adequate activation of the peripheral apparatus, as evidenced by preserved reflex vestibular nystagmus in response to head motion. In a recent study, we reported VA in acute TBI (aTBI) patients, most of whom were also imbalanced. We localised the overlap between imbalance and VA in aTBI patients to damage in the inferior longitudinal fasciculus in the right temporal lobe. We postulate however, that the brain networks whose disconnection mediate VA per se are widespread, including that of bilateral posterior cortical regions processing sensory vestibular signals and

recurrent tracts linked to anterior regions mediating perceptual 'ignition' of self-motion sensation. We assessed white matter tract connectivity using probabilistic tractography with a region of interest (ROI) approach in 25 aTBI patients, 11 of those aTBI were classified as having VA (VA+) while 14 as not having VA (VA-) using normative self-motion perceptual thresholds of 37 healthy control subjects. Initial ROI-based tractography analyses of white matter tracts for VA+ vs. VA- aTBI patients show: (i) differences in white matter tract count between right and left hemispheres of the cerebellum and superior longitudinal fasciculi; (ii) changes in volume and length of the superior and inferior longitudinal fasciculi; (iii) distinctions in DTI scalar measures indicating axonal damage, including fractional anisotropy (FA), axial diffusivity (AD), mean diffusivity (MD) and radial diffusivity (RD). Future analyses will include exploration of i) diffusivity measures from the angular gyri and right temporo-parietal junction ii) study of axonal fibre connectivity (afd) to determine fibre connectivity in desired ROI(s) iii) analysis of variance to examine group differences in mean diffusivity and AFD results iv) linear regression to examine the relationship between diffusivity measures, axonal fibre connectivity (AFD) and balance performance across patient and control groups. In summary, the preliminary results suggest that white matter abnormalities are aggravated in the presence of vestibular agnosia, thus impacting connectivity of vestibular networks.

Object-specific visual and semantic representations contribute to subsequent true and false recognition: an fMRI study with RSA

Unique Code: TP001346

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Topic: Computational and theoretical neuroscience

Introduction

Visual properties of the world and semantic properties of our knowledge base are proposed to make distinct contributions to accurate memory and memory distortions. In this preregistered functional magnetic resonance imaging (fMRI) study (https://osf.io/ypmdj), we used representational similarity analysis (RSA) to uncover the representations involved in true and false recognition of objects.

Methods

Twenty-eight participants made name judgements about images of objects during scanning, and later had to discriminate studied items from similar lures and novel objects. We modelled distributed brain activity in 6 regions of interest (ROIs) using two representational dissimilarity models (RDMs) capturing semantic similarity via specific object features and coarse taxonomic domains, and two models of perceptual similarity indexing early visual and color attributes.

Approach for statistical analysis

In each ROI we extracted multivoxel activity for trials that were subsequently remembered -forgotten (TrueSM), or subsequently falsely recognized - correctly rejected (FalseSM). We calculated pairwise similarity per trial with Pearson correlation. We created separate RDMs incorporating contrasts of TrueSM and FalseSM for each model. RDMs were fit to fMRI data using Fisher-transformed Spearman rank correlation and subjected to two-tailed Fisher's one-sample randomization (10,000 permutation) T-tests at Bonferroni alpha over 6 ROIs.

Results and conclusion
Low-level visual attributes coded in early visual and posterior ventral temporal cortex, including lingual and fusiform gyrus, were associated with successful object encoding. In fusiform gyrus the object-specific semantic feature model also predicted true recognition, while coarse taxonomic semantic representations in bilateral ventral anterior temporal lobe, left perirhinal cortex, and left inferior frontal gyrus predicted forgetting. In contrast, later false recognition was related to weak low-level visual representations in early and late visual cortex. Our data show that detailed visual information promotes true recognition and lure correct rejection. However, whether semantic representations boost or impede accurate encoding depends on accessing fine versus coarse semantic information.

Exploring the Effectiveness of Machine Learning and EEG for Predicting Pain Intensity, Phenotypes and Treatment Response: A Systematic Review

Unique Code: TP001359
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Topic: Computational and theoretical neuroscience

Research applying machine learning (ML) and Electroencephalogram (EEG) for the prediction of pain-related outcomes has demonstrated exciting results that may assist clinical pain care. We aimed to systematically review the literature relating to the effectiveness of ML and EEG for classifying pain intensity, phenotypes and treatment response. Electronic databases MEDLINE, EMBASE, Web of Science, PsycINFO and The Cochrane Library were searched, identifying 38 eligible studies for review. Here, 19 studies investigated pain intensity prediction, 13 attempted to classify pain phenotypes, and six attempted to predict response to treatment. The results show that pain intensity, phenotypes and treatment response can be identified with accuracies ranging between 62% to 100%, 57% to 96.15% and 65% to 95.24%, respectively. Overall, the results are promising, suggesting that ML and EEG could be used in-tandem to predict pain-related outcomes. Further research and clinical validation would increase the clinical potential of ML, which could contribute to improved pain care.

Disorders, treatments and translational neuroscience

A stitch in time saves nine - comparative analysis of spinal dural tear repair surgery

Unique Code: TP001020
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Topic: Disorders, treatments and translational neuroscience

Introduction: A dural tear is a common neurological complication of spinal surgery and can cause a variety of post-operative complications. Despite the relatively common occurrence of this intra-operative complication there are no definitive clinical guidelines on how best to repair the defect. This study compares the dural-tear repair methods used to treat 106 intra-operative dural tears sustained in Southampton General Hospital between 01/01/2016 and 04/11/2019 to determine which method is associated with the greatest clinical outcomes.

Methods: Data was collected from Southampton General Hospital's 'Charts', 'E-documents' and 'Surgical complications'

databases. 106 confirmed intraoperative dural tears were identified within the date range. Patients were grouped per their repair method.

Approach for statistical analysis: A MANOVA was used to compare the following 5 variables between repair types: Length of original stay, length of additional stays, numbers of further admissions or surgeries required, post-operative infection rate and dural tear associated neurological symptoms. Sub-analysis was then conducted on the type of patches used, primary closure vs non-primary closure, patient demographics and they type of surgeries that caused the dural tears.

Results and conclusion: Primary repair ± a patch was found to be the most advantageous form of repair. The incidence of dural tears was 5.81% and they were most common in emergency operations (56%) and at the L4/L5 spinal level. Statistical significance was achieved when comparing the use of artificial versus autologous patches in favour of artificial patches. Age was also shown to have a statistically significant impact on post-operative outcomes, with elderly patients having worse outcomes ($p<0.001$). Although statistical significance was not reached, primary closure was found to be the most advantageous form of repair with respect to 4 out of 5 of the observed outcomes of this study.

Influence of Transcutaneous Vagal Nerve Stimulation on Brain Activity: A Meta-analysis of Neuroimaging Evidence

Unique Code: TP001025

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Topic: Disorders, treatments and translational neuroscience

Introduction

Dysautonomia plays a central role in disease pathophysiology for a number of neurological and psychiatric conditions but due to complex underpinning mechanisms, limited options exist for their medical management. Considering the pivotal role of the vagus nerve in the central autonomic network, transcutaneous vagal nerve stimulation (tVNS) has been proposed as a novel therapeutic intervention which might restore this disease-driven autonomic disruption. However, the brain regions involved in the tVNS mediated effects remain unclear.

Objective

To identify the reproducible neural correlates activated by tVNS by meta-analysis of previously published data.

Methods

Synthesising all available brain imaging data, we conducted a meta-analysis to identify the best approximation of the brain effects of tVNS. A total of 157 studies were identified from the Web of Science and PubMed databases, 4 of which met the inclusion criteria for neuroimaging-based statistical analysis, which provided data on 60 subjects (17 male, 27 female and 16 not provided) aged 18-45.

Approach for Statistical Analysis

Using activated likelihood analysis estimation, we established brain activity changes from tVNS statistically contrasted to both null and sham stimulation. All analyses used a cluster-forming threshold of $p < 0.05$, a corrected cluster-level inference threshold of $p < 0.05$ and a permutation threshold of 5000.

Results

tVNS consistently increased activity in the bilateral insula, left thalamus, bilateral frontal pole, bilateral anterior cingulate cortex, right putamen, bilateral caudate and bilateral central opercular cortex and reduced activity in the bilateral parahippocampal gyri, bilateral hippocampi, bilateral temporal occipital fusiform gyrus and right posterior cingulate cortex (all $p<0.005$ or lower).

Conclusion

tVNS reproducibly alters activity in brain areas implicated in pain processing, emotional regulation and in the regulatory central autonomic network. The central role of dysautonomia in the multiple neurological and psychiatric pathologies, coupled with the prior clinical success of tVNS in these disease contexts, indicates that further therapeutic exploration of this intervention is warranted.

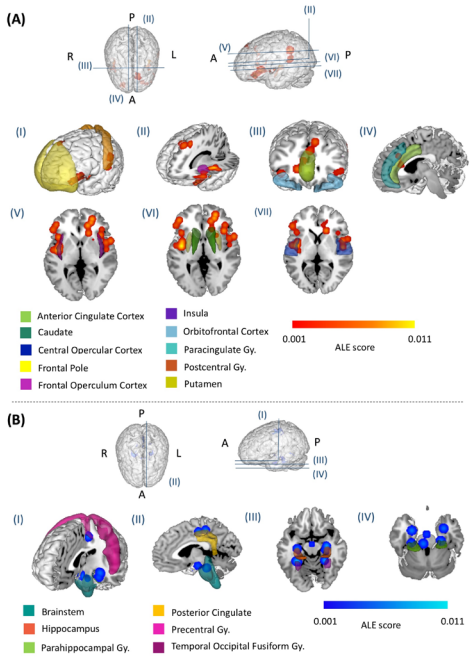

Figure 1: Results of the ALE analysis showing brain regions associated with (A) increased activity tVNS vs. no stimulation and (B) decreased activity tVNS vs. no stimulation. Abbreviations: A, anterior; ALE, activated likelihood estimation; L, left; P, posterior; R, right.

Transcranial Doppler ultrasonography as a tool for preclinical study of migraine treatments

Unique Code: TP001036

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Topic: Disorders, treatments and translational neuroscience

Introduction. Migraine is a common neurovascular disorder associated with activation of the trigeminovascular system. Several studies reported a reduction of blood flow velocity in the middle cerebral artery (MCA) in the early stage of a migraine attack, indicating that Doppler ultrasonography may be useful for investigating migraine-related processes. Here, we aimed to explore if transcranial dopplerography can be adopted in preclinical research of migraine treatments. Accordingly, we used a rat model of acute trigeminovascular activation and assessed the sensitivity of changes in Doppler indices to established anti-migraine drugs.

Methods. End-diastolic velocity, peak systolic velocity, systolic-diastolic velocity ratio, pulsatility index, and resistive index in the MCA of 26 anaesthetised rats were recorded before, during, and after electrical stimulation of the exposed dura mater. MCAs with a notable and persistent decrease in end-diastolic velocity in response to the stimulation were selected for further testing. The animals received cumulative infusions of valproate (n = 8, 100 mg/kg, trice), sumatriptan (n = 8, 0.3, 1, and 3 mg/kg) or saline (n = 10) in 20-min intervals. The dural stimulation with measurement of Doppler indices was repeated every 10 min for 1 hour.

Approach for statistical analysis. A mixed-effects ANOVA followed by pairwise comparisons with Tukey's multiplicity adjustment where appropriate.

Results and conclusions. At baseline, electrical stimulation of the dura mater induced changes in all measured indices ($p < 0.001$, compared to pre-stimulation values), but peak systolic velocity. End-diastolic velocity decreased by a median of 20.3%, interquartile range, 27.9 – 16.8%, while systolic-diastolic velocity ratio, pulsatility index, and resistive index increased by a median of 13.2 – 24,7% of pre-stimulation values. The revealed changes, however, diminished over time independent of treatment. These results do not support the idea of using transcranial Doppler ultrasonography as a tool for preclinical study of migraine treatments, at least in the model of acute trigeminovascular activation.

Interneuron vulnerability underlying epilepsy in Alpers-Huttenlocher syndrome

Unique Code: TP001037
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Topic: Disorders, treatments and translational neuroscience

Introduction: Alpers-Huttenlocher syndrome (AHS) is a fatal paediatric mitochondrial disease resulting from depletion of mitochondrial DNA and characterised by intractable epilepsy and severe neurodegeneration. Dysfunction and degeneration of inhibitory interneurons due to deficits in mitochondrial respiratory complex subunits is hypothesised to underlie seizure-associated alterations in cortical activity. However, it is not known whether particular subclasses of interneurons are vulnerable in AHS.

Methods: Post-mortem brain tissues were obtained for the occipital cortex (BA17) from 11 AHS patients and were

compared to 7 age-matched controls. Immunohistochemistry was performed to identify parvalbumin (PV), calretinin (CR), calbindin (CB) and somatostatin (ST)-positive interneurons and neuronal densities were quantified. Quadruple immunofluorescence permitted visualisation and quantification of expression of mitochondrial respiratory complexes I and IV subunits (NDUFB8 and COXI, respectively) within mitochondria (porin) in PV and CR interneurons.

Approach for statistical analysis: All data were log-transformed to achieve normality. Control interneuron density and control respiratory chain data were used to derive z-scores in order to make inferences about interneuron loss and interneuron dysfunction, respectively, in AHS. Classifications were based on standard deviation limits: z<-2SD = low; z<-3SD = deficiency, z<-4SD = severe deficiency.

Results: There was a severe, consistent loss of PV interneurons in 9 of 11 patients, with a relative preservation of CR interneurons. However, the loss of CB and ST interneurons was highly variable. To investigate whether mitochondrial dysfunction underlies the vulnerability of PV interneurons relative to CR interneurons in AHS, the expression of NDUFB8 and COXI were measured in PV and CR interneurons. NDUFB8 and COXI were deficient (z<-4) in 87% and 96% of PV interneurons, respectively. Whereas NDUFB8 and COXI were deficient in 32% and 11% of CR interneurons, respectively.

Conclusion: There is a severe, selective loss of PV interneurons and severe respiratory chain impairment within remaining PV interneurons within BA17. This could result in loss of inhibitory neurotransmission leading to seizures in patients with AHS.

The effect of PEDOT:PTS coating in DBS electrode impedance and LFP recording quality in vivo and in silico

Unique Code: TP001054

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Topic: Disorders, treatments and translational neuroscience

Introduction

Recordings with chronically implanted neural electrodes deteriorate over time. PEDOT:PTS coating has been shown to improve recording quality in vitro and up to 2 wks in vivo. Here impedance and local field potentials (LFPs) recorded from coated and platinum iridium(PtIr) electrodes chronically implanted in rats for 8 wks were compared and models of the corresponding electrode-tissue interfaces developed.

Methods

PtIr or PEDOT:PTS coated PtIr electrodes were implanted in the basal ganglia of 12 rats. Impedance spectra were recorded 3/wk and LFPs were recorded at implantation, 4 and 8 wks. Experiments fulfilled Irish ethic and licensing requirements.

Experimental impedance data were used in combination with a 3D-finite element rat brain model to estimate electrical properties of the encapsulation tissue and electrode electrical double-layer(EDL). LFPs at the electrode were simulated

using a model of basal ganglia synaptic currents coupled to the finite element model.

Approach for statistical analysis
Normally distributed impedance data were compared using two-way repeated-measures ANOVA. For LFP data, power spectra were estimated and signal-to-noise ratio calculated. Data were compared using the Mann-Whitney test. Criterion for significance: $P<0.05$; power: 80%. Pre-study calculation showed a minimum sample size was 6/group.

Results and conclusions
From 3-8wks the impedance of PtIr electrodes was significantly higher(60kΩ) than of coated electrodes(20kΩ). The LFP signal-to-noise-ratio was similar for both at implantation($P=0.51$), but higher in coated electrodes at 4 and 8 wks (5.2 vs. 31.1, $P<0.05$).

Modelling confirmed that the contribution of electrode tissue impedance to the LFP power spectrum was dominated by the EDL which was characterised by lower impedance for the coated electrodes, with increased EDL capacitance. The simulated LFP data using coated electrode properties showed increased amplitude when compared with uncoated electrodes, similar to the experimental data.

The results confirm that PEDOT:PTS can increase signal quality via modification of the EDL of chronically implanted recording electrodes.

Mitochondrial dysfunction in parvalbumin interneurons leads to early-onset neurological symptoms associated with mitochondrial disease in vivo

Unique Code: TP001057
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Topic: Disorders, treatments and translational neuroscience

Introduction: Mitochondrial diseases comprise the largest group of inherited metabolic disorders. Neurological symptoms include epilepsy, stroke-like episodes, ataxia and cognitive impairment. This study aims to model early-onset neurological symptoms in mitochondrial disease using a novel murine model and to test the hypothesis that underlying hyperexcitability may arise due to neuronal network disinhibition, following mitochondrial dysfunction in parvalbumin-expressing (PV+) inhibitory interneurons.

Methods: A mouse model of mitochondrial DNA depletion specifically within the PV+ cells was generated by a knockout of mitochondrial transcription factor A (Tfam) and characterised at behavioural, electrophysiological, neuropathological and molecular levels. Neuronal network activity was probed within the hippocampus CA3 area in vitro by inducing gamma oscillations using carbachol (cholinergic agonist). GABAergic function was assessed using a GABA-A receptor antagonist.

Approach for statistical analysis: Shapiro-Wilk normality test was applied to all data sets. If passed normality test,

parametric statistical tests were utilised (unpaired student's t-test; ANOVA with post-hoc testing). If normality test was failed, non-parametric tests (Mann-Whitney U test; Kruskal-Wallis with post-hoc testing) were used instead. Fisher's exact test was applied to compare proportions between groups. A P-value < 0.05 was deemed significant.

Results and conclusions: A downregulation of complexes I, III and IV of the mitochondrial respiratory chain was confirmed within the PV+ cells of the knockout brain tissues. Homozygous knockout mice exhibited phenotype at 8 weeks of age starting with tremor, cognitive impairment (assessed by novel object recognition test) and anxiety behaviour (in the elevated plus maze test), progressing to hyper-locomotion (in the open field test) and stargazing (absence seizures) at 10 weeks, leading to severe ataxia by 12-13 weeks (rotarod test). Electrophysiological analysis of mutant mice revealed hippocampal network perturbation. The novel mouse model recapitulates the early-onset phenotype of mitochondrial disease and highlights the role of mitochondrial function within the PV+ inhibitory interneurons.

Effects of folic acid treatment on neonatal hypoxia-ischemia model

Unique Code: TP001062

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Topic: Disorders, treatments and translational neuroscience

Neonatal hypoxia-ischemia (HI) is a major cause of death and chronic disability worldwide. Preterm newborns are highly vulnerable due to having the immature antioxidant defence systems, and often exhibit clinical manifestations such as motor and memory deficits. Previous studies have suggested that the antioxidant activity of folic acid (FA) could have protective effects on HI model. The aim of this study was to evaluate whether FA treatment could improve neurological and metabolic complications from neonatal HI. Wistar rats were divided into four groups (CT, CT-FA, HI and HI-FA) and submitted do HI procedure, in which consists of a permanent ligation of artery common carotid on seven-day-old rat pups. Treatment include the administration (I.P.) of FA (0.011uM/g body weight) for 14 days. Then, it was performed ox-maze task (n=11-12 per group), oxidative stress parameters (nitrite and sulfhydryl) (n=6-7 per group) and epigenetic marker as histone deacetylase (HDAC) activity (n=4-6 per group) on the hippocampus. Two-way analysis of variance (ANOVA) and Tukey's post-test were used when indicated considering $p \leq 0.05$. All procedures were approved by the Ethical Committee at the UFRGS, Brazil (nº 23564). Results showed that HI animals untreated had increased latency, time to complete the task and number of incorrect nose pokes when compared to controls on ox-maze task. Also, fewer correct nose pokes it was observed in the HI animals untreated compared to controls, highlighting that HI caused memory and learning impairments. Furthermore, it was observed that FA animals had alleviated deficits in some parameters as latency and total time in the task compared to untreated animals (HI-S) during testing days. Regarding the effects of FA treatment, on some parameters of oxidative stress, neither nitrite levels nor total sulfhydryl content showed a significant difference between groups. In addition, epigenetic marker, HDAC has not changed its activity between groups. In conclusion, the HI model showed a learning impairment, which was partially reversed by FA. Taken together, the results indicate that other parameters should be evaluated, as well as pathways involved in the formation of oxidative stress and neuronal death.

Tonic activity facilitates striatal dopamine release during burst activity which is non-linearly related to intracellular calcium concentration

Unique Code: TP001063

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Topic: Disorders, treatments and translational neuroscience

Dopamine neurons play critical roles in reinforcement learning and action selection. Dopamine neurons spontaneously fire and have tonic low frequency and phasic high frequency spike activity at the cell body level. However, axons of dopamine neurons are not passive cables that faithfully convert neuronal activity into dopamine release. Ex vivo studies in mouse striatum show that isolated high-frequency stimuli (100Hz) evoke dopamine release approximately linearly for small pulse numbers (n>4), whereas intermittent low-frequency stimulation (≤40Hz) shows short-term depression in dopamine release.

However, it is unclear how an ongoing background of tonic activity, as seen in vivo, impacts on how axons convert activity into dopamine release. To address this question, we applied a tonic-like electrical stimulation (2Hz, 6 pulses) before a burst stimulation in ex vivo striatal slices from mouse brain. During tonic stimulation, dopamine release showed a strong initial depression and rapidly decreased to a steady level. Subsequent burst-evoked dopamine on a background of tonic activity was facilitated in a supra-linear manner with stimulation frequency. We investigated whether this supra-linear increase corresponds to calcium entry. By imaging GCaMP6f in dopamine axons, we found that calcium entry did not mirror the dopamine release pattern. There was no initial depression in calcium signals during tonic activity, and there was a sub-linear relationship between calcium entry and intra-burst frequency. A background of tonic activity had minimum impact on calcium entry during a burst. These findings indicate that calcium entry more efficiently triggers dopamine release during a high-frequency stimulation when a background of tonic activity is present.

These findings reveal that tonic activity in dopamine neurons modulates the activity-dependence of dopamine during burst activity. These findings will revise our understanding of dopamine function during phasic activity, such as in encoding reward-prediction errors. They also suggest that despite the potential energetic burden of handling Ca2+ entry to extensive arbors of dopamine axons, there are gains in function that enable greater levels of dopamine release to occur for a given level of intracellular calcium.

Electrophysiological Signature of Blast Injury in the Rat Auditory Cortex

Unique Code: TP001096

Authors: John Goodwin - Department of Bioengineering Imperial College London, Michael Bruyns-Haylett - Department of Bioengineering Imperial College London, Andrei S. Kozlov - Department of Bioengineering Imperial College London,

Topic: Disorders, treatments and translational neuroscience

Introduction: Recent conflicts in the Middle East have left scores of veterans with hearing damage and blast induced traumatic brain injury (bTBI). Evidence suggests that whilst the peripheral hearing system may heal with time, lasting damage to the central auditory system (CAS) may make more complex tasks such as differentiation between competing speakers more challenging. In particular, CAS processing deficits can progress and become more apparent over time. In

this investigation, we assess CAS processing deficits in the months following bTBI, with the aim of better understanding the progression of the pathology through the CAS.

Methods: Male Sprague Dawley rats were exposed to a 230kPa Friedlander pressure wave perpendicular to the head under isoflurane anaesthesia. Animals then recovered, and at time-points 1 and 3 months post blast, animals were placed under urethane anaesthesia and Local field Potentials (LFP) from the primary auditory cortex were recorded during presentation of complex auditory stimuli: a single ultrasonic vocalisation (USV) source, and a 'cocktail party' stimulus of competing USV sources. Two second sections of LFP and the log of the envelope of the stimulus were cross correlated, and grand-average correlations were calculated as a function of lag. The peak correlation value and peak lag time were compared.

Approach for statistical analysis: As neural activity may randomly correlate with the stimulus envelope at a certain delay, randomising with respect to delay gives an approximate normal distribution of correlation values, from which a 95% threshold is set. The Fisher Z-transformation was used to convert correlations to z-values and one-way ANOVA was used to compare peak correlation and lag time respectively.

Results and conclusions: Evoked responses in the primary auditory cortex showed a mean peak positive correlation lagging the stimulus by 79ms across all groups. An ANOVA test showed no significant differences in peak lag time or peak correlation between the two stimuli at 1-month post blast, but at 3-months post blast the peak correlation was significantly lower for the cocktail party stimulus compared to the single USV stimulus. This may be a sign of a developing deficit in the CAS's ability to track complex stimuli.

Associatively activated stimulus representation and reality testing in a rodent model of psychotic disorders

Unique Code: TP001100
Authors: Sophie Waldron - Psychology Cardiff University,
Topic: Disorders, treatments and translational neuroscience

Introduction
There are assays for negative and cognitive symptom domains in animal models of psychotic disorders; yet assessing positive symptoms such as hallucinations remains a challenge. Learning about associatively activated stimulus representations may allow for assessment of 'hallucination-like' behaviour in rodents (Dwyer, 2018). After two neutral stimuli are associated, exposure to one should activate a representation of the other. Associatively activated representations can support learning if paired with a consequence (mediated conditioning, Holland, 1998). Holland (1998) proposed that associatively activated stimulus representations are initially processed perceptually, yet with overtraining they will be processed conceptually. Perceptual representations are expected to support mediated conditioning while conceptual representations are not. But with rodent models of positive symptom pathology representations may remain in the perceptual stage allowing for mediated conditioning even after extended training (Schoenbaum et al 2011). This prediction was tested on the Dlg2+/- rat model of genetic risk for schizophrenia (Kirov et al., 2012).

Methods
Water-restricted Dlg2+/- and wild-type rats were trained to drink water in a neutral context (A) before receiving either 4

or 8 pairings of one flavour (sucrose or saline) with context B and the other in context C. Rats were then re-exposed to context B immediately preceding LiCl induced illness. Mediated learning of flavour-illness associations was assessed through consumption of flavours in neutral context A.

Approach for statistical analysis
The analysis used a combination of traditional mixed model ANOVA and Bayesian ANOVA with within-subjects factors of flavour valance (negative if its associated context was paired with illness and positive if not) and between subjects factors of genotype, sex and the number of flavour-context pairings.

Results & Conclusions
Mediated conditioning was similar after 4 and 8 pairings in both Dlg2+/- and wild-type rats. This contrasts with Holland's (1998) proposals of a change from perceptual to conceptual processing across training and implies that under-expression of Dlg2 may not contribute to positive symptoms such as hallucinations.

Possible Association between Creutzfeldt-Jakob Disease and Cancer: A Genome-Based Investigation

Unique Code: TP001108
Authors: Arif Kamil Salihoglu - Physiology Karadeniz Technical University, Faculty of Medicine,
Topic: Disorders, treatments, and translational neuroscience

INTRODUCTION: Creutzfeldt–Jakob Disease (CJD) is a rare and rapid-progressive neurodegenerative prion disease, accompanied by neuropsychiatric symptoms, painful sensations, involuntary movements, dementia, coma and ultimately death. The disease has four subtypes: sporadic, familial, variant and iatrogenic. Sporadic CJD (sCJD) is the most common form presenting 85% of CJD cases. Pathogenesis of CJD is not fully determined and there is no specific treatment. In addition to clnical studies, recent evidences indicates hope from CJD from in silico analysis. The aim of this study was to detect possible pathophysiological factors in CJD on examining the expression levels of genes by using bioinformatics tools.

METHODS: GSE156994 dataset obtained from GEO (Gene Expression Omnibus) database was re-examined for this research. In the dataset, 114 sCJD and 105 control DNA samples derived from human blood is recruited. After the gene expression levels in the dataset were re-analysed in the R program, gene set enrichment analyses were performed in Gene Ontology (GO) and ENRICHR tools.

APPROACH FOR STATISTICAL ANALYSIS: Expression levels of genes, commonly implicated to play a role in several biological processes, in GSE156994 dataset are re-analysed in R program. Based on Benjamini-Hochberg correction, adjusted p-values <0.05 were accepted as significant.

RESULTS AND CONCLUSION: Gene expression levels indicated that human epidermal growth factor receptor 3 and 4 (ERBB3, ERBB4), MYC and SRC proto-oncogenes, breast cancer type 1 (BRCA1), retinoblastoma (RB1), fibroblast growth factor receptor 1 (FGFR1), interleukin 6 signal transducer (IL6ST) genes were up-regulated ($p<0.05$); and BCL2 associated X-apoptosis regulator (BAX), phosphatase and tensin homolog (PTEN) and nuclear factor kappa B subunit 2 (NFKB2) genes were down-regulated ($p<0.05$) in sCJD group, compared with control group. Likewise, significant expression differences were detected in over 100 carcinogenesis-related genes. Although there is no clinical clue that CJD has an aspect with cancer development, these results implicate that these related genes may be prognostic precursor markers

of CJD, and the source of neurological manifestations.

Keywords: Creutzfeldt-Jakob disease, neurodegeneration, bioinformatics.

Altered cortical DNA methylation in a rodent model for schizophrenia suggests programmed changes in neurodevelopment and neuronal signalling processes

Unique Code: TP001113

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Topic: Disorders, treatments and translational neuroscience

Introduction: Maternal immune activation (mIA) is a risk factor for schizophrenia (SZ) but the underlying causative mechanisms are unknown. We model this paradigm by exposing pregnant rats to the viral mimetic, poly(I:C), inducing mIA and adult offspring cognitive deficit. We hypothesise that mIA directly influences fetal neurodevelopment via maladaptive epigenetic changes and have investigated offspring developmental changes in global DNA methylation.

Methods: On gestational day (G) 15 pregnant Wistar rats received i.p. poly(I:C) or control saline, and plasma cytokine concentrations were measured. DNA was extracted from isolated offspring cortices (at G21 and postnatal day (P) 21, 35, 175) and analysed by a global methylation ELISA. We assessed adult offspring in the attentional set shifting task (ASST) for executive function, and analysed DNA methylation profiles from assessed females by reduced representation bisulphite sequencing (RRBS). Sequence reads were aligned to reference genome rn5.0 (Bismark v0.20.0), differential methylation analysis performed (Methylkit v1.7.0) and differentially methylated CpGs (DMCs) and regions (DMRs) annotated with R package, annotatr.

Statistical approach: We used the general linear mixed model to analyse plasma cytokines, ASST scores and global methylation data. Pairwise comparison for poly(I:C) versus control was used to identify DMC/Rs, and logistic regression used to compare percentage methylation between groups. P-values were corrected to q-values using the sliding window model with $q<0.01$ and >25% methylation difference as a cut-off.

Results and conclusions: Poly(I:C) treatment increased maternal plasma IL-6 ($p=0.06$) and TNF-α ($p=0.001$), and induced ASST deficits in adult female offspring ($p=0.007$). Global methylation was increased in G21 to P35 mIA-offspring, while RRBS identified 22096 DMCs and 3227 DMRs, mapped to 4029 genes. Gene ontology demonstrated enrichment in neurodevelopmental and neuronal signalling pathways. Further analysis demonstrated expression enrichment in the cerebral cortex and highlighted genes with genetic/epigenetic variants in neurological disorders, including SZ. Our data support a mechanistic relationship between mIA, altered DNA methylation of cortical genes and adult cognitive deficit.

Pupillary Light Reflex and Pupillary Unrest as Biomarkers of Parkinson's Disease: A Systematic Review and Meta-Analysis

Unique Code: TP001127

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Topic: Disorders, treatments and translational neuroscience

Introduction

The prodromal pathological processes leading to Parkinson's Disease (PD) begin decades before the onset of motor symptoms. Objective biomarkers may allow for early detection and monitoring of the condition. Autonomic dysfunction is one of the main non-motor manifestations of PD, however, the utility of autonomic measures as biomarkers remains unknown. The pupillary light reflex (PLR) and pupillary unrest are under autonomic control and thus might provide an automated and non-invasive index of PD prodrome. This work aims to systematically review studies comparing pupillary responses to light and pupillary unrest between PD patients and healthy controls to critically evaluate these metrics as potential biomarkers of PD.

Methods

Search strategy to report PLR and pupillary unrest results in patients with PD was optimised using three databases (MEDLINE, EMBASE, PsycINFO) with cross-references from identified papers and Google Scholar. The last date of literature search was 7 December 2020.

Approach for Statistical Analysis

Pupillometric measures which allowed for statistical pooling of results were maximum constriction velocity (VMax), constriction amplitude (CAmp) and constriction latency (CL). Pooled incidence and outcome measures were calculated through a random effects model employing an inverse variance DerSimonian-Laird estimator. Study heterogeneity was appraised through the I^2 statistic and analyses were performed in Stata V16. Where meta-analysis was not possible, qualitative analysis was conducted.

Results and Conclusions

The primary search yielded 219 references. Following deduplication and exclusions, 31 papers were reviewed. Pupillometric outcomes from 11 articles were included in meta-analysis (Figure 1). VMax, CAmp and CL showed significant main effect size for PD patients of -0.85 ($p<0.01$), -0.61 ($p=0.02$) and 0.40 ($p=0.03$) respectively. Pupillary unrest measures were higher in PD than in controls, however, the evidence was limited to 2 studies. Pupil metrics offer a promising avenue for early detection of PD. However, these findings are limited by heterogeneity in pupillometric methodologies and disease duration. Further large-scale cohort studies are required to validate these measures as quantitative biomarkers of PD.

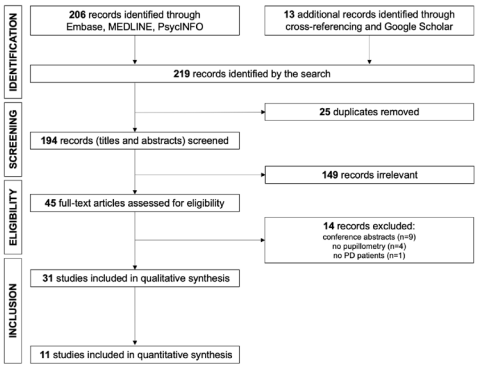

Figure 1. PRISMA flow diagram detailing exclusions throughout each stage of study selection.

A systematic review of cerebral phenotypes associated with mutations in the HTRA1 gene

Unique Code: TP001132

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Topic: Disorders, treatments and translational neuroscience

Introduction

Cerebral small vessel disease (cSVD) causes stroke, with an increasing burden in the ageing population. cSVD develops due to a combination of environmental and genetic factors. A minority of individuals undergo genetic testing for a mutation in the NOTCH3 gene, which causes CADASIL. However, several other Mendelian cSVD genes have been reported, including HTRA1. HTRA1 is not routinely tested in clinical practice, and hence less is known about its associated phenotype. We aimed to summarise the cerebral phenotypes associated with mutations in the HTRA1 gene.

Methods

We performed a systematic review (PROSPERO CRD42020196720) searching Medline/Embase for publications of any language describing individuals with mutation(s) in HTRA1 (defined here as ‘cases’). We extracted information about their cerebral phenotypes and compared homozygous/compound heterozygous (HomZ) to heterozygous (HetZ) cases.

Approach for statistical analysis

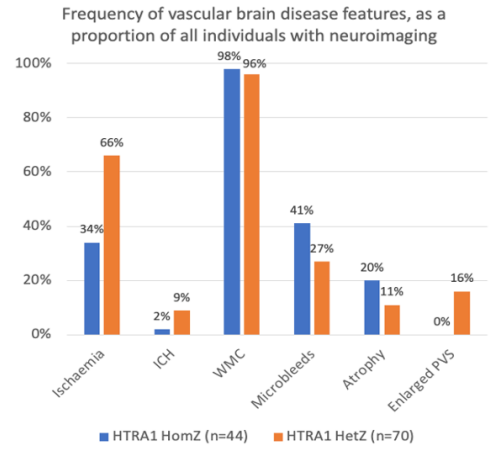
We compared baseline characteristics and frequencies of associated phenotypes between HomZ and HetZ cases. We used $\chi 2$ test for categorical variables and independent sample t-test for continuous variables.

Results and conclusions

We screened 6485 publications and included 60, totalling 44 HomZ and 82 HetZ HTRA1 cases. HetZ cases were older than HomZ (mean ages 59 and 35 years, respectively; p<.0001) and had more frequently suffered a stroke (60% and

29%, respectively; p=.014). Cognitive decline was common (64% HomZ, 56% HetZ), as were psychiatric features (32% HomZ, 23% HetZ). Among those with neuroimaging (114/126; 90%), >99% cases had ≥1 typical cSVD change (Figure). White matter changes (WMC) were the commonest manifestation (96% HetZ, 98% HomZ). HetZ cases more frequently had ischaemia compared to HomZ (66% and 34%, respectively; p=.001). Enlarged perivascular spaces were only reported in HetZ cases (16%). There were no significant differences in the frequency of haemorrhage, microbleeds or atrophy.

We conclude that HTRA1 mutation cases present mostly with cSVD on neuroimaging. There appear to be differences in the cerebral manifestations of HomZ and HetZ cases, but this may be an age effect or relate to other biases in the existing literature. Future work will examine the cerebral phenotypes of other cSVD genes.



HomZ = homozygous/compound heterozygous; HetZ = heterozygous; n = number; ICH = intracerebral haemorrhage; WMC = white matter change; PVS = perivascular space

Subcommissural organ-spondin-derived peptide restores memory in a mouse model of Alzheimer's disease

Unique Code: PP001387

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Topic: Disorders, treatments and translational neuroscience

Alzheimer's disease (AD) is a neurodegenerative disease affecting million people who suffer from the progressive deterioration of cognitive functions including learning and memory. The few approved treatments such as donepezil are limited to the symptomatic control of AD, therefore there is an urgent need to develop a disease-modifying treatment to halt AD-induced cognitive deficits. The subcommissural organ (SCO)-spondin is a brain-specific glycoprotein which contributes to neuronal development. Here, we sought to evaluate the protective effects of the linear (NX210) and cyclized (NX210c) forms of a SCO-spondin-derived peptide on learning and memory in a mouse model of AD.

Mice were subjected to an intracerebroventricular injection of Aβ25-35 oligomers and treated with intraperitoneal injections of vehicle, NX210 or NX210c according to different doses (ranging from 0.1 to 30 mg/kg) and therapy paradigms (early or late stand-alone treatments, combination with donepezil or second-line treatment). Cognitive functions were evaluated using the Y-Maze, the step-through latency passive avoidance (STPA) and the Morris water maze (MWM) tests for up to 4 months.

One- and two-way ANOVA followed by Tukey's comparisons test were used for graphs containing groups with normal distributions and group variances. Otherwise, a Kruskal-Wallis followed by a Dunn's comparisons test was applied.

Early-stage daily treatment with NX210 and NX210c decreased the levels of common markers of AD such as Aβ1-42, phosphorylated Tau and TNF-α, and increased synaptogenesis. Regardless of the experimental paradigm used, NX210 and NX210c prevented AD-induced decreased spontaneous alternations (Y-Maze) and step-through latency into the dark compartment (STPA), and AD-induced increased time to find the immersed platform during the learning phase and decreased time in the target quadrant during the retention phase (MWM). This study provides the first evidence that the native and oxidized cyclic forms of a SCO-spondin-derived peptide reduce common hallmarks of AD pathology and restore learning and memory at both early and late pathological stages. Overall, we shed light on the therapeutic potential of this innovative disease-modifying peptide to restore memory function in AD patients.

Effects of phytocannabinoids on microRNA expression in two models of generalised epilepsy

Unique Code: TP001138

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Topic: Disorders, treatments and translational neuroscience

Introduction

Epilepsy is one of the most common neurological diseases. There is an urgent need for new therapies for drug-resistant epilepsy. Recently, the non-psychoactiv phytocannabinoid cannabidiol (CBD) has been approved for the treatment of rare childhood epilepsies including Dravet syndrome (DS). The mechanism by which CBD exerts its anti-seizure effects is not fully known. MicroRNAs (miRNA) are small non-coding RNAs which regulate protein expression. Their expression is highly altered in epilepsy and targeting certain miRNAs can prevent seizures. We hypothesised that modulation of miRNAs is a potential mechanism of action for the therapeutic effects of CBD. To test this, we measured changes to the levels of miRNAs in the hippocampus of mice after dosing with CBD using a regime known to produce anti-seizure effects.

Methods

We first identified a dose of CBD that produced acute anti-seizure effects in the pentylenetetrazol (PTZ) mouse model. Then, adult male C57BL/6 mice were treated for five days twice daily with CBD (200 mg/kg/d; i.p.) or vehicle control. Mice were euthanised and the hippocampus processed for small RNA sequencing. A selection of differentially expressed miRNAs were validated using individual Taqman miRNA assays and levels of the miRNAs were measured using hippocampus from a mouse model of DS (Scn1a+/-).

Approach for statistical analysis

Data were analysed for normal distribution using D'Agostino and Pearson omnibus normality test. For the statistical analysis, a Kruskal-Wallis with post hoc Dunn's multiple comparison test or unpaired t-test was performed and data was considered significant at $p \leq 0.05$.

Results and conclusions
A dose of 200mg/kg caused a significant reduction in seizure severity in the PTZ model. Using this dose, CBD treatment produced changes to 66 miRNAs in the mouse hippocampus ($p<0.05/0.01$; non-FDR corrected). This included 20 up-regulated and 46 down-regulated miRNAs, including lower levels of miR-335. Analysis of the hippocampus from the DS mouse revealed levels of the same miRNA were increased. In summary, these data demonstrate that CBD treatment at a dose that produces anti-seizure effects results in selected changes to miRNAs in the brain of mice that may have relevance for its anti-seizure mechanism.

Probenecid increases the concentration of 7-chlorokynurenic acid derived from the prodrug 4-chlorokynurenine within the prefrontal cortex

Unique Code: TP001156

Authors: Waseema Patel - Department of Pharmacology and Therapeutics University of Liverpool, Lara Rimmer - Department of Pharmacology and Therapeutics University of Liverpool, Martin Smith - Department of Pharmacology and Therapeutics University of Liverpool, Lucie Moss - Department of Pharmacology and Therapeutics University of Liverpool, Mark A Smith - VistaGen Therapeutics, Inc VistaGen Therapeutics, Inc, H. Ralph Snodgrass - VistaGen Therapeutics, Inc VistaGen Therapeutics, Inc, Munir Pirmohamed - Department of Pharmacology and Therapeutics University of Liverpool, Ana Alfirevic - Department of Pharmacology and Therapeutics University of Liverpool, David Dickens - Department of Pharmacology and Therapeutics University of Liverpool

Topic: Disorders, treatments and translational neuroscience

Introduction: Depression is a mood disorder that is a leading cause of disability worldwide. The prodrug of 7-chlorokynurenic acid (7-Cl-KYNA), 4-chlorokynurenine (4-Cl-KYN), has failed to show efficacy in recent clinical trials, possibly due to inadequate accumulation of 7-Cl-KYNA in the brain. Thus, we sought to characterise the passage of 4-Cl-KYN and 7-Cl-KYNA across the blood-brain barrier (BBB) to determine how we could boost the brain concentration of 7-Cl-KYNA.

Methods: We used radiolabelled 4-Cl-KYN and 7-Cl-KYNA to follow the uptake of these compounds into HEK293 cells expressing transporters on the BBB. We also used microdialysis studies in Sprague-Dawley rats to determine how the concentrations of 4-Cl-KYN and 7-Cl-KYNA in the prefrontal cortex (PFC) were affected by their transport.

Approach for statistical analysis: Analyses were carried out on Graphpad Prism v8; uptake assays were analysed by one-way ANOVA and microdialysis data was analysed using two-way ANOVA or an unpaired t-test.

Results and Conclusions: We found 4-Cl-KYN to be a substrate of the L-type amino acid transporter (LAT1; SLC7A5); 4-Cl-KYN (250µM) uptake increased to 7126 ± 824 pmoles/million cells in HEK293-LAT1 cells vs 1046 ± 28.3 pmoles/million cells in control cells ($n=3$, $p<0.05$). 7-Cl-KYNA (2µM) was found to be a substrate of organic anion transporter 3 (OAT3; SLC22A8, 32.6 ± 5.6 pmoles/million cells vs 1.0 ± 0.4 pmoles/million cells in control cells, $n=3$, $p<0.05$). The OAT3 inhibitor probenecid, prevented this uptake of 7-Cl-KYNA via OAT3 (1.4 ± 0.4 pmoles/million cells, $n=3$, $p<0.05$). Moreover, co-expression of multidrug resistance protein 4 (MRP4; ABCC4) with OAT3 showed MRP4 was responsible for 7-Cl-KYNA efflux (5.1 ± 0.4 pmoles/million cells vs 23.2 ± 1.3 pmoles/million cells in HEK293-OAT3 cells, $n=3$, $p<0.05$). Furthermore, microdialysis studies showed coadministration of 4-Cl-KYN with probenecid caused an 885-fold increase in 7-Cl-KYNA within the PFC compared to 4-Cl-KYN alone. Thus, we show that 4-Cl-KYN crosses the BBB via LAT1 whilst 7-Cl-KYNA is exported by OAT3 and MRP4. We also found probenecid coadministration increased the concentration of 7-Cl-

KYNA within the PFC, possibly boosting the therapeutic effect of 4-Cl-KYN.

Funded by VistaGen Therapeutics, Inc

Convergence Insufficiency, Vestibulo-Ocular Reflex, Eye-Blink Rate and Ocular Tremor as Biomarkers of Parkinson's Disease: A Systematic Review

Unique Code: TP001176

Authors: Emilia Violet Butters - Solvemed Group, Aleksander Dawidziuk - Faculty of Medicine Imperial College London, Maja Wojtynska - Faculty of Medicine Imperial College London, Anna Kiepura - Faculty of Life Sciences University College London, Hugo Chrost - Solvemed Group ,Michal Wlodarski - Solvemed Group ,John Grogan - Nuffield Department of Clinical Neurosciences University of Oxford, Paulina A Rowicka - Solvemed Group ,Sanjay Manohar - Nuffield Department of Clinical Neurosciences University of Oxford

Topic: Disorders, treatments and translational neuroscience

Introduction

Parkinson's Disease (PD) is well characterised by its motor symptoms, however, various non-motor symptoms, such as visual disturbances, may appear in prodromal stages. Deficits in various parts of the visual processing system have been reported in PD patients, partly relating to the dopamine deficiency present in PD. At the brainstem level, ocular tremor, and convergence insufficiency (CI), as well as deficits in vestibulo-ocular reflex (VOR) and eye-blink rate (EBR), have been observed, however, the value of these measures as potential biomarkers for PD has yet to be systematically assessed. The present systematic review seeks to critically evaluate the literature and assess the value of these four measures for early diagnosis and monitoring of PD.

Methods

Search strategy to report convergence, VOR, EBR and ocular tremor results in PD patients was optimised using three databases (MEDLINE, EMBASE, PsycINFO). The last date of this literature search was 7 December 2020.

Approach for Statistical Analysis

Based on the heterogeneity in reporting of the outcomes by the included articles and insufficient numbers of articles for each measure, pooled analysis of quantitative results could not be performed. The Newcastle-Ottawa Scale was used to assess the quality of the studies.

Results and Conclusions

The primary search identified 3588 records. Following deduplication and exclusions, 27 studies were included in qualitative synthesis with 10 articles reporting outcomes for convergence, 7 for VOR, 6 for EBR and 5 for ocular tremor (Figure 1). Objective measures of CI were significantly different in PD patients compared to controls, including significantly lower convergence amplitudes (seen in 2/2 studies), greater near point of convergence (3/5) and higher convergence latency in PD patients (1/1). Additionally, self-reported CI symptoms yielded significantly higher scores in PD (2/2). The reported outcomes for VOR, EBR and ocular tremor lacked consistency. Quantitative oculomotor indices of brainstem function present an opportunity for early detection and quantitative characterisation of PD. However, this review highlighted the need for further cohort studies with standardised reporting to evaluate these measures as potential biomarkers for PD.

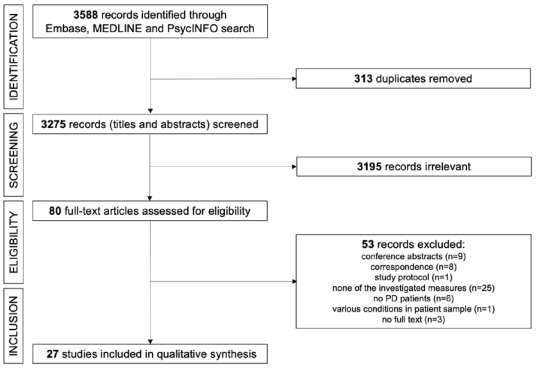

Figure 1. PRISMA flow diagram detailing exclusions throughout each stage of study selection.

Murine neural stem cells cultured on marine collagen 3D scaffolds retain key regenerative features

Unique Code: TP001185

Authors: Anthea Mutepfa - School of Life Sciences Keele University, Christopher Adams - School of Life Sciences Keele University,

Topic: Disorders, treatments and translational neuroscience

Spinal cord injury (SCI) is a serious condition caused by damage to the spinal cord through trauma or disease, often with permanent debilitating effects. Despite a lack of effective treatments for SCI, cell therapy remains as the most promising option. The advent of biomaterials has increased the potential of cell therapy through improving cell survival and retention. Whilst medical grade mammalian collagen biomaterials exist for applications such as wound healing, marine collagen (MC) presents as an alternative to the latter in that it carries no risk of bovine spongiform encephalopathy transmission, has similar immunogenicity and is more sustainable. However, it has yet to be tested for neural applications. In this study, we investigated the potential of Jellagen®, a MC biomaterial, in maintaining key regenerative features of neural stem cells (NSCs) including viability, proliferation and differentiation. It was hypothesized that Jellagen® would not affect the regenerative features of NSCs compared to standard glass controls.

NSCs were obtained from P0-P3 mice and expanded as neurospheres in culture. The cells were plated and maintained in monolayer medium for 5 days on glass controls and Jellagen® scaffold slices. A viability assay, proliferation assay and immunocytochemistry was performed to compare the health and characteristics of the cells. A subset of the NSCs were induced in differentiation medium for a further 7 days prior to performing the viability assay, proliferation assay and immunocytochemistry.

Descriptive statistics were obtained and the control and experiment groups were compared to each other using unpaired t-tests. A p value of <0.05 was considered statistically significant. Data was analysed from n=6, where n is an individual repeat from a biological litter.

The cells on Jellagen® substrates showed a high viability comparable to the controls. Differentiation was not affected and proliferation followed similar trends in both groups. For the first time we report data that suggests that MC does not affect NSC viability, proliferation and differentiation compared to the standard control in 2D culture. The data supports the future exploration of MC as a medical grade biomaterial for SCI cell transplant populations.

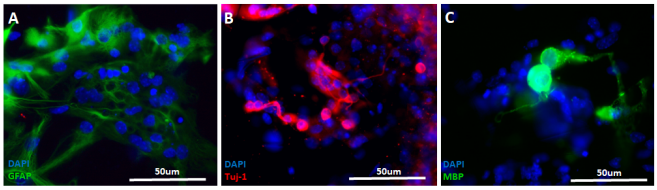

Figure 1: Neural stem cells cultured on Jellagen substrates were induced in differentiation medium for 7 days and were shown to express markers for astrocytes (A), neurons (B) and oligodendrocytes (C).

The noble gas xenon is neuroprotective following severe controlled cortical impact neurotrauma in rats

Unique Code: TP001191

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Topic: Disorders, treatments and translational neuroscience

Introduction: Traumatic brain injury (TBI) is a significant global healthcare burden. Clinical practice for TBI patients is largely supportive, centred on non-specific endpoints such as management of tissue oxygenation, cerebral perfusion pressure and intracranial pressure[1]. There are no clinically validated drug treatments aimed specifically at preventing neuronal loss following TBI. Xenon is a noble gas used as a general anaesthetic and in MRI imaging[2]. We showed that xenon-treatment improves short and long-term outcomes, prevents late-onset cognitive impairments and improves survival after moderate TBI in mice[3, 4]. This study evaluates the efficacy of xenon in a second species, rats, and in a severe injury model.

Methods: Adult male Sprague Dawley rats (N=22) underwent controlled cortical impact (CCI) brain trauma or sham surgery. Animals were randomised to receive 50%Xe:25%O2:25%N2 or 75%N2:25%O2. Locomotor function (CatwalkXT) and histological outcomes [lesion volume, neurons (NeuN), microglia (Iba1) and astrocytes (GFAP)] were assessed by blinded observers. Statistical significance was assessed using ANOVA with Sidak's test (locomotor function), Mann Whitney test (lesion volume) or Kruskal Wallis test with Benjamini Yeukateili correction (NeuN, Iba1, GFAP).

Results & Conclusions: The control CCI group exhibited locomotor deficits that were reduced in the xenon group. Lesion volume was reduced in the xenon group. Xenon-treatment resulted in preservation of neurons in cortical and subcortical regions associated with increases in numbers of resting microglia and reactive astrocytes.

We show for the first time that xenon is neuroprotective after severe TBI in rats. Functional improvement and neuronal preservation is associated with xenon-induced enhancement of resting microglial cell numbers and astrocyte activation. These findings are consistent with a role for early beneficial neuroinflammation in xenon's neuroprotective effect. Xenon may be of benefit in the treatment of clinical brain trauma.

1. Hutchinson, P.J., et al BMJ, 2013. 346: p. f1000
2. Dickinson, R. et al Crit Care, 2010. 14(4): p. 229
3. Campos-Pires, R., et al., Crit Care Med, 2015. 43(1): p. 149-158
4. Campos-Pires, R., et al., Br J Anaesth, 2019. 123(1): p. 60-73

Is it all in our head? When subjective beliefs about receiving an intervention predict results better than the intervention itself

Unique Code: TP001192

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Topic: Disorders, treatments and translational neuroscience

Recently, there has been debate about the effectiveness of psychological interventions (e.g., non-invasive brain stimulation (NIBS), neurofeedback, cognitive training) due to contradictory findings. Up to date, studies in these fields usually compare the effects of an active form of the intervention to a placebo/control condition. However, a neglected question is how to consider individual differences in response to blinding procedures and their effect on behaviour, rather than merely compare the efficacy of blinding using a group-based approach. The present study aims to address this gap by examining how variations in subjective beliefs about NIBS, one of the most recent and popular intervention methods, affect research outcomes. To this aim, we suggest using subjective intervention—the participants' subjective beliefs about receiving or not receiving an intervention—as a factor. Specifically, we examined whether subjective intervention and subjective dosage (i.e. participants' subjective beliefs about the intensity of the intervention they received) affected performance scores independently, or interacting with, the objective intervention (the actual condition to which participants were assigned in the study). We analysed an open-access dataset that has shown the efficacy of active NIBS in altering mind wandering. In specific, we run model comparison using bayesian ANOVA as a statistical approach. Results showed that subjective intervention and subjective dosage - alone- successfully explained alterations in mind wandering better than the objective intervention. These findings point to the importance of accounting for participants' beliefs about receiving interventions at the individual level by demonstrating their effect on behaviour independently of the objective intervention. Altogether, our study highlights a neglected issue that is likely to impact the validity of conclusions in previous basic and clinical research and provides an approach to allow more rigorous study design and analysis for NIBS and non-NIBS intervention.

Novel biomarker to predict the development of axial symptoms in Parkinson's

Unique Code: TP001196

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Topic: Disorders, treatments and translational neuroscience

Introduction:
Axial symptoms within Parkinson's (PD) are common and include freezing of gait (FOG), impaired gait and postural instability. The combination of these symptoms is known as postural instability and gait disorder (PIGD). The Pedunculopontine Nucleus (PPN) is involved in walking and postural stability, and is implicated in PIGD. In PD, it has been shown that people with PIGD have degeneration within the PPN, particularly the right PPN. Here, we used neuroimaging to investigate whether changes in the right PPN could predict future development of axial symptoms from very early PD stages.

Methods:
146 newly diagnosed participants with PD underwent Diffusion Tensor Imaging (DTI) at baseline. Stereotactic mapping

was used to investigate the microstructure of the PPN. Participants were followed up for 72-months at 3- and 6-month intervals, and instances of axial symptoms were recorded via the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III assessment.

Statistical analysis:
Univariate analyses were used to compare microstructural metrics between PD participants with and without axial symptoms. A survival analysis was used to investigate whether increased degeneration within the right PPN could successfully predict the development of axial symptoms.

Results:
At baseline, participants who developed PIGD, FOG, and postural instability over the follow-up period had evidence of greater changes in the microstructure of the right PPN. This degeneration in the right PPN could also predict which participants were at risk of developing PIGD, impaired gait, and postural instability, over and above clinical and demographic variables. However, FOG was not predicted by the microstructural changes of the right PPN.

Conclusions:
These results suggest that the microstructure of the right PPN is a novel neuroimaging biomarker for predicting certain axial symptoms in PD. Earlier identification of axial symptoms will allow for earlier interventions and optimal treatment. Better management of axial symptoms has the potential to reduce fall-related injuries and loss of independence in people with PD.

The contribution of the cholinergic basal forebrain and pedunculopontine nucleus to cognitive deficits in Parkinson's disease

Unique Code: TP001198

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Topic: Disorders, treatments and translational neuroscience

Introduction: The pedunculopontine nucleus (PPN) degenerates in Parkinson's, but how this affects cognitive and motor symptoms is not clear. The PPN's cholinergic projections to thalamus, basal ganglia, cerebellum, and other brain regions imply a role in functions that go beyond the traditional view of the nucleus as purely a locomotor control region. However, investigations in humans are limited by the region's brainstem location and small size. More is known about the brain's other cholinergic nucleus (the cholinergic basal forebrain; cBF), which is known to contribute to cognitive symptoms in both Parkinson's and Alzheimer's disease. But we lack a full understanding of the combined function of the

PPN and cBF, limiting our understanding of how they may be targeted by pro-cholinergic interventions.

Methods: We used diffusion tensor imaging (DTI), along with stereotactic mapping, to investigate microstructure of the PPN and cBF. Ninety-eight participants with early Parkinson's disease and 40 controls underwent a comprehensive neuropsychological assessment and had artefact-free DTI scans available at baseline as part of the longitudinal ICICLE-PD study. Cognitive assessments were repeated at 18-month intervals for a maximum of four study visits.

Statistical analysis: Pearson's correlations and linear mixed modelling (LMM) were used to investigate relationships between microstructural metrics from the cBF and PPN, and cognitive scores, controlling for age, sex, and whole brain microstructure.

Results and conclusions: We found robust correlations between reaction-time-based attention tasks and microstructural metrics in both the cBF and PPN at baseline in participants with Parkinson's. In LMMs, these metrics could also predict longitudinal decline in attention. Interestingly, there was an independent contribution to progression of attention deficits from both the PPN and cBF.

Our findings confirm the role of the PPN in functions that go beyond control of locomotion. Our data support the suggestion that the PPN is involved in attentional tasks that require rapid responses and imply that degeneration of the PPN and cBF may make independent contributions to attentional decline. Targeting the PPN and cBF together could be an effective strategy for restorin

Does impaired nucleus accumbens function underlie deficits in reward-motivated behaviour in the Df(16)A+/- mouse model of 22q11.2 deletion syndrome?

Unique Code: TP001199

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Topic: Disorders, treatments and translational neuroscience

Introduction: Deletions within the 22q11.2 locus influence cognitive impairments and are highlighted to increase risk for psychiatric disorders. Df(16)A+/- mice containing this microdeletion show deficits in associative and spatial learning, including the T-maze delayed non-match to position task (DNMS). Although this deficit has been linked to prefrontal cortical (PFC)–hippocampal synchrony, the association between this genetic variant on reward/food-motivated behaviours remains unknown.

Methods: Sixty-six male and female adult mice (Wildtype; n=31, Df(16)A+/-; n=35) underwent a behaviour battery including open field (OF), elevated-zero maze (EZM), social interaction (SI), novel object recognition (NOR) and T-maze (DNMS). For the latter, mice were food restricted to 90% bodyweight, with 50%-diluted condensed milk used as a reward. The same reward was given 60min prior to tissue collection, with brains dissected and drop-fixed in 4% paraformaldehyde to allow immunohistochemistry processing of c-fos in regions associated with motivation, feeding, and reward in mice.

Results: Df(16)A+/- mice elicit increased ambulatory activity ($p<0.05$) with females showing slightly more activity

compared to males (p=0.095). However no significant differences were found in the EZM, SI or NOR tests. In the T-maze, Df(16)A+/- mice required significantly more sessions to learn the pattern of forced alternation (p<0.001), but also showed less motivation for food rewards (p<0.001) despite successful habituation. Initial immunostaining indicates reduced c-fos counts/mm2 in the nucleus accumbens (p<0.001) following a reward (further results pending).

Conclusion: Df(16)A+/- mice are known to have impairments in PFC-HPC synchrony, which will underlie at least some of the poor working memory performance. However, non-schizoprenic 22q11.2 individuals also show impairment in reward-motivated learning, so our results may provide some insights into the neurobiological basis of this deficit. Understanding this relationship could provide insight into the role of the 22q11.DS on anhedonia and motivational deficits in mice, which may hold translational value for disorders such as schizophrenia.

A single injection of HBK-15 reverses depressive-like behaviours in the unpredictable chronic mild stress in mice

Unique Code: TP001204

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Topic: Disorders, treatments and translational neuroscience

Introduction: Antidepressants, even those recently discovered, are effective in only half of the patients. Moreover, current treatments often take weeks or months to achieve therapeutic effects. HBK-15, a multimodal compound, showed significant antidepressant-like, anxiolytic-like, and memory-enhancing properties in rodent tests in our previous experiments. Given the promising results, in this study, we aimed to evaluate the antidepressant-like activity of a single administration of HBK-15 in the mouse model of unpredictable chronic mild stress.

Method: All experiments were performed using male CD-1 mice. We used the unpredictable chronic mild stress model of depression to determine antidepressant-like activity, with the forced swim test, sucrose preference test, and locomotor activity test as behavioural endpoints. Next, we collected prefrontal cortices and hippocampus to determine the level of BDNF, p-CREB, p-CaMKIV, pp-PKA, and p-ERK1/2 using the ELISA method.

Approach for statistical analysis: We analyzed the data using one-way ANOVA, with Newman-Keuls post hoc. The experimental unit was the individual animal, and each animal was allocated to a particular treatment group independently of other animals.

Results and conclusions: We observed a significant increase in immobility and reduced preference for sucrose solution in chronically stressed mice receiving saline compared with non-stressed controls (Fig. 1A-B). Locomotor activity was not altered (Fig. 1C). A single administration of HBK-15 reversed an increase in immobility and reduced preference for sucrose in the stressed mice (Fig. 1A-B). HBK-15 upregulated the decreased levels of BDNF p-CREB, p-CaMKIV, p-PKA, p-ERK1/2 in the stressed mice (Fig. 1D-H).

We found that a single administration of HBK-15 reversed depression-like behaviours and regulated decreased BDNF and p-CREB levels in the prefrontal cortex and hippocampus in the stressed mice. The transcription factor CREB was activated via several pathways, i.e., p-CaMKIV, p-PKA, and p-ERK1/2. Our results suggest that HBK-15 has the potential to be a model structure for next-generation antidepressants. This study has been conducted as part of a research project financed by the National Science Centre, Poland (grant 2019/34/E/NZ7/00454).

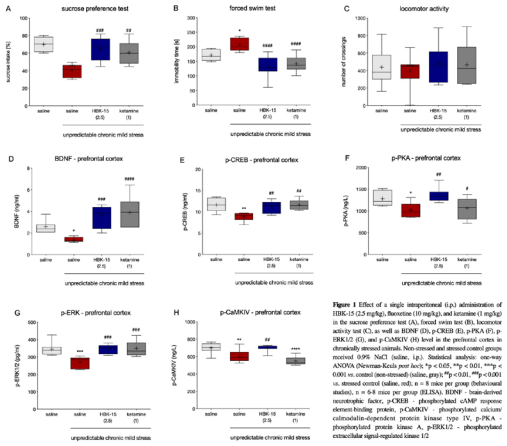

Figure 1 Effect of a single intraperitoneal (i.p.) administration of HBK-15 (2.5 mg/kg), fluoxetine (10 mg/kg), and ketamine (1 mg/kg) in the sucrose preference test (A), forced swim test (B), locomotor activity test (C), as well as BDNF (D), p-CREB (E), p-PKA (F), p-ERK1/2 (G), and p-CaMKIV (H) level in the prefrontal cortex in chronically stressed animals. Non-stressed and stressed control groups received 0.9% NaCl (saline, i.p.). Statistical analysis: one-way ANOVA (Newman-Keuls *post hoc*): *p < 0.05, **p < 0.01, ***p < 0.001 vs. control (non-stressed) (saline, grey); #p<0.01, ###p<0.001 vs. stressed control (saline, red); n = 8 mice per group (behavioural studies), n = 6-8 mice per group (ELISA). BDNF - brain-derived neurotrophic factor, p-CREB - phosphorylated cAMP response element-binding protein, p-CaMKIV - phosphorylated calcium/calmodulin-dependent protein kinase type IV, p-PKA - phosphorylated protein kinase A, p-ERK1/2 - phosphorylated extracellular signal-regulated kinase 1/2

Substrate-induced clustering enables selective degradation of expanded poly-glutamine by TrimAway

Unique Code: TP001230

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Topic: Disorders, treatments and translational neuroscience

Trim-Away is a powerful new technology that can acutely and rapidly degrade proteins using intracellular antibodies and the E3 RING ligase and cytosolic antibody receptor TRIM21. How TRIM21 is catalytically-activated upon substrate engagement is unknown. Here, we aimed to determine the mechanism of TRIM21 activation. Using antibodies against an artificial substrate containing a repeated epitope sequence we show that it takes a threshold number of antibodies to be bound to the substrate in question to activate degradation via TRIM21. We further investigated whether TRIM21 and antibodies can be used for the selective degradation of host proteins implicated in neurodegeneration as a research tool and as a potential therapeutic strategy. Indeed, we demonstrate that expanded poly-glutamine tracts can be specifically degraded at the protein level, while leaving wildtype length tracts unaffected. Statistical significance based on two-tailed Student's t-tests.

Our results demonstrate that, like other antibody receptors, TRIM21 is activated by ligation of polyvalent immune complexes. This mechanism provides a novel strategy for the selective depletion of cytoplasmic proteins with broad research and therapeutic implications.

HBK-15, a 5-HT1A receptor ligand with memory-enhancing properties, preferentially activates ß-arrestin signaling

Unique Code: TP001234

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Topic: Disorders, treatments and translational neuroscience

Biased agonists preferentially activate certain signaling pathways. Therefore, they might offer novel treatment strategies, i.e., show pharmacological activity without inducing unwanted effects. As our research proved that 1-[(2-chloro-6-methylphenoxy)ethoxyethyl]-4-(2-methoxyphenyl)piperazine hydrochloride (HBK-15) display rapid antidepressant-like properties in rodents, here, we investigated the memory-enhancing activity, as well as the possible functional selectivity of HBK-15, a compound with high affinity for 5-HT1A receptors.

We used various cell-based functional assays to determine the intrinsic activity of HBK-15 at the 5-HT1A receptor, i.e., influence on cAMP production, phosphorylation of ERK1/2, and ß-arrestin recruitment. To determine the possible procognitive properties of HBK-15, we induce the memory deficits in mice by acute MK-801 injection. Then, we performed the novel object recognition test and passive avoidance test to assess long-term episodic-like and emotional memory, respectively, and the rotarod test to determine motor skill learning. Moreover, we investigated the compound's effect on the three necessary stages in the learning and memory process: encoding, consolidation, and retrieval.

We analyzed the data using one-way ANOVA, with Bonferroni post hoc or one-sample t-test. The experimental unit was the individual animal, and each animal was allocated to a particular treatment group independently of other animals.

We demonstrated that the efficacy and potency of HBK-15 varied between the signaling pathways. The compound showed functional selectivity at the 5-HT1A receptor, i.e., it preferentially activated ß-arrestin signaling. Moreover, HBK-15 presented procognitive activity in behavioral tests. However, HBK-15 did not normalize MK-801-induced motor learning and memory.

Although it is not yet clear to what extent functional selectivity can be exploited for therapeutic advantage, some clinically used drugs like carvedilol (ß-blocker) or oliceridine (opioid) show this effect. Therefore, compounds with functional selectivities, such as HBK-15, are worth investigating. This study has been conducted as part of a research project financed by the National Science Centre, Poland (grant 2019/34/E/NZ7/00454).

Baseline sacral nerve morphometry and cystometry in a sheep model used for development of a sacral neuroprosthesis to detect urinary bladder pressure

Unique Code: TP001244

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Department of Electronic and Electrical Engineering University of Bath, Richard J Piercy - Clinical Science and Services The Royal Veterinary College, Nicolas Granger - Clinical Science and Services The Royal Veterinary College,
Topic: Disorders, treatments and translational neuroscience

Introduction
Managing urinary bladder retention in humans with spinal cord injury is vital to reduce kidney damage. Voiding is restored by implantation of the Finetech-Brindley neuroprosthesis that stimulates anterior sacral roots. However, this requires posterior root rhizotomy to prevent reflex incontinence, eliminating remaining sexual function. A neuroprosthesis that avoids rhizotomy, by detecting bladder pressure and in turn blocking reflex incontinence, is desirable. Bladder pressure has been determined from sacral root electrical activity in anaesthetised rats; for translation, development of an implantable device in a freely moving animal is required. We report baseline sacral nerve morphometry and cystometry data in a sheep model.

Methods
Four female sheep underwent cystometries (Medica PicoSmart urodynamic system) at a fill rate of 50ml/min while anaesthetised, and later awake. Five further sheep had sacral roots (S1-4) exposed by dorsal laminectomy with stimulation of the roots at 30Hz from 1-20V using a Finetech stimulator with bipolar electrodes. The bladder was pre-filled with saline to 20cmH2O and the maximum bladder pressure rise recorded. S1-4 were collected post-mortem, semi-thin sectioned and toluidine blue stained. Nerve fibre morphometry was performed on 40x whole-root images using semi-automated ImageJ analysis.

Statistical analysis
Descriptive statistics: mean ± SD. Analysis of stimulation by mixed effects model, compliance by 2-way ANOVA.

Results and Conclusions
Conscious cystometry was well-tolerated. Bladder compliance was 3.2±1.8ml/cmH2O, significantly lower than the same animals under anaesthesia (6.8±4.5ml/cmH2O; $F(1,26)=12$, $p=0.0002$).

Intraoperative unilateral electrical stimulation of S2 and S3 caused a 10±6 and 11±7cmH2O increase in bladder pressure respectively, significantly greater than the response from S1 (1±1cmH2O [$F(3,87)=19$, $p<0.0001$; post-hoc Tukey $p<0.0001$]) but not significantly different to S4 (4±4cmH2O).

Sacral root morphometry is presented in Fig. 1 showing fibre count and size distribution in each root.

We provide important baseline values to compare histological change in the nerve roots after implantation of a sacral neuroprosthesis, and assess sacral root response to bladder pressure in sheep.

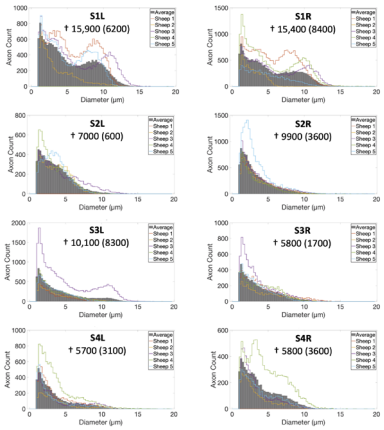

Figure 1. Morphometric analysis of bilateral sacral roots S1-4 from 5 sheep. Mean fibre size distribution histogram shown in grey, overlaid with individual animals in colour for each extra-dural sacral root. † Mean (SD) total fibre count.

Transplantation of hydrogel encapsulated olfactory ensheathing cells expressing chondroitinase ABC for chronic spinal cord injury in companion dogs

Unique Code: TP001248

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Topic: Disorders, treatments and translational neuroscience

Introduction

Olfactory ensheathing cells (OECs) and chondroitinase ABC (chABC) separately improve walking recovery in rats and pet dogs after spinal cord injury (SCI). We have genetically modified OECs to express chABC (OEC-chABC) which can improve forepaw reaching in rats with cervical SCI. Encapsulating OECs in collagen hydrogel increases their survival after transplant. Here we present a pilot study of hydrogel encapsulated autologous OEC-chABC transplant in pet dogs with chronic SCI, a compressive-contusive SCI model that could help translate OEC-chABC to the clinic.

Methods

Four paraplegic dogs >3 months after SCI were recruited. Baseline neurological examination (including electronic von Frey assessment), olfactory mucosa biopsy, spinal MRI, blood and lumbar CSF samples were obtained. OEC cultures were transduced with a 3rd generation lentivirus to express chABC. Proportion of p75+ cells (OECs) was determined prior to transplant and chABC secretion confirmed by Morgan Elson reaction. Cystic SCI lesion cavity volume was calculated from MRI and OEC-chABC were encapsulated in an equal volume of liquid hydrogel before percutaneous, fluoroscopy guided intraspinal transplant at lesion epicentre and 1 segment cranial and caudal. MRI was repeated immediately after injection. Dogs received regular neurological examination for 6 months and MRI, blood and CSF sampling was repeated once at 2-3 months.

Statistical analysis

Descriptive statistics are median (range). MRI volume and von Frey analysis by 2-way repeated measures ANOVA.

Results and Conclusions
A median of 3.95 (1.8 – 6.5) million cells, with 46% (7 – 99%) OECs were transplanted; all expressed chABC. Pre-transplant lesion volume was 396mm3 (301-464mm3) with highly varied morphology between dogs. This volume did not change significantly after transplant.

Neurological examination remained unchanged during the trial, although owners reported changes in reflexive hind limb activity and urinary continence. No significant change was seen on haematology, biochemistry or CSF cytology. No hypersensitisation was detected by electronic von Frey.

We therefore suggest that hydrogel-encapsulated autologous OEC-chABC transplant in paraplegic dogs is safe, and a randomised-control efficacy trial feasible.

Valproic Acid Attenuates Seizures And Extends Lifespan Of The Zebrafish Model Of CLN2 Disease

Unique Code: TP001260
Authors: Claire Russell - Comparative Biomedical Sciences Royal veterinary College, Rebecca Martin-Jimenez - Faculte des Sciences Universite de Moncton, Fahad Mahmood - General Surgery University Hospitals Birmingham NHS Foundation Trust, Anselm Zdebik - Neuro, Physiology and Pharmacology University College London, Alexandra Au - Emergency Lap of Love Veterinary Hospice, Jennifer Cooke - Comparative Biomedical Sciences Royal Veterinary College,Kate Bennett - AcureOmics AB AcureOmics AB, Izabella Surowiec - AcureOmics AB AcureOmics AB, Katrin Lundstedt-Enkel - AcureOmics AB AcureOmics AB, Torbjorn Lundstedt - AcureOmics AB AcureOmics AB, Michelangelo Campanella - Comparative Biomedical Sciences Royal Veterinary College
Topic: Disorders, treatments and translational neuroscience

Introduction
CLN2 disease is a type of neuronal ceroid lipofuscinosis and a lysosomal storage disorder causing progressive neurodegeneration, epilepsy and premature death in children. Our zebrafish model of CLN2 disease has a mutation in tpp1 (encoding the lysosomal protease Tripeptidyl-peptidase-1) and replicates the genetics, neurodegeneration and lysosomal storage. We hypothesize that tpp1-/- zebrafish display electrical and behavioural evidence of seizure activity that responds to established anti-convulsants.

Methods
tpp1sa0011-/- and normal siblings treated with carrier, 20mM (electroencephalography) or 5mM (all other assays) valproic acid, or 20mg/ml Pentobarbitone-Na were assessed for seizures using single electrode electroencephalography, locomotion using Ethovision software, survival analysis, apoptosis using a TUNEL assay, lysosomal storage using Lysotracker, and GABA using immunofluorescence. Metabolites were measured using GC-MS.

Approach for statistical analysis
Kruskal Wallis tests were performed for all data except lifespan (Kaplan Meier) and metabolomics (Jackknife confidence intervals (OPLS-DA modelling) or t-test).

Results and Conclusion
To demonstrate seizures we performed electroencephalography showing tpp1-/- zebrafish had increased spiking activity versus normal siblings with significantly increased amplitude about 2-4Hz. This was attenuated by valproic acid ($p<0.05$),

but not pentobarbitone. Valproic acid also significantly reduced tpp1-/- seizure-related movement bouts ($p<0.05$) and distance moved ($p<0.05$), thereby correlating movements to seizures. Valproic acid significantly extended the lifespan of tpp1-/- with mortality between 3-6 days post-fertilization of 8.33% when valproic acid-treated vs 33.3% when untreated ($p=0.01$). A decrease in apoptotic bodies ($p<0.001$) and lysosomes ($p<0.05$) was seen in valproic acid treated tpp1-/- compared to untreated. GABA levels were increased by valproic acid treatment in tpp1-/- ($p<0.05$). Metabolomics showed that Threonine and Lactic Acid levels are corrected by valproic acid in tpp1-/- ($p<0.05$). These results indicate the mechanisms by which valproic acid may be improving not only seizure liability, but also survival.

FLAME trial: Exploring the feasibility of recruitment and recommendations for trials involving people with epilepsy

Unique Code: TP001264

Authors: Cheney Drew - Centre for Trials Research Cardiff University,

Topic: Disorders, treatments and translational neuroscience

INTRODUCTION: Pre-clinical studies have suggested that fluoxetine can restore cognitive deficits found in models of temporal lobe epilepsy (TLE). FLAME (Fluoxetine, Learning and Memory in Epilepsy) was a feasibility trial investigating the efficacy of fluoxetine treatment in improving memory and learning impairments in people with TLE. We aimed to recruit 20 people to receive either fluoxetine or placebo and undergo memory and cognitive testing.

METHODS: Potential participants were assessed for eligibility according to the trial inclusion/ exclusion criteria. At the conclusion of the trial, interviews were conducted with; those who took part in the study, those who were invited but declined, self-referred participants and clinicians involved in recruitment to better understand reasons for and barriers to participation.

ANALYSIS: Feasibility was determined by rates of recruitment, retention and adherence according to pre-specified criteria. Interviews were audio recorded, transcribed verbatim and analysed thematically.

RESULTS AND CONCLUSIONS: 26 out 151 invitees replied positively. Of these, 13 were screened for inclusion and 6 assessed as eligible. 5 participants were randomised and completed the trial. According to pre-specified recruitment criteria, FLAME trial was not found to be feasible. All other feasibility measures (retention and adherence) satisfied the progression criteria.

22 people were interviewed including 3 clinicians, 4 trial participants, 3 self-referrals and 12 who declined to participate. The majority of interviewees expressed an altruistic interest in participating in epilepsy research. From those that declined to participate the main reasons cited were a reluctance to take fluoxetine (due to perceived risk or stigma), the time commitment involved and travel required. However, some of those who initially declined to participate expressed a contemporary interest in joining the trial.

Recruitment to clinical trials is problematic and those involving people with epilepsy experience particular difficultly. Views from potential trial participants suggest that we need to design trials to be more sympathetic to the circumstances of those we wish to include in research. We advocate enhanced public and patient involvement to achieve this

Transient ultrasound stimulation has lasting effects on neuronal excitability

Unique Code: TP001268

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Topic: Disorders, treatments and translational neuroscience

Background:
Transcranial ultrasound stimulation can acutely modulate brain activity, but the lasting effects on neurons are unknown. We assessed the excitability profile of neurons in the hours following transient ultrasound stimulation.

Methods:
Primary rat cortical neurons were stimulated with a 40 second, 200kHz pulsed ultrasound- or sham-stimulation. Intrinsic firing properties were investigated through whole-cell patch-clamp recording by evoking action potentials in response to somatic current injection. Recordings were taken at set timepoints following ultrasound stimulation: 0-2 hours, 6-8 hours, 12-14 hours and 24-26 hours. Transmission electron microscopy was used to assess synaptic ultrastructure at the same timepoints.

Statistical Analysis:
Data was tested for normality by D'Agostino and Pearson K2 test ($p < 0.01$). Non-normal data was analysed by Mann-Whitney U test. Normally distributed data was analysed by either two tailed unpaired t-test, 2-way analysis of variance (ANOVA), or mixed-effects model. Holm-sidak method was used for between group (i.e., control vs ultrasound) multiple comparisons testing.

Results:
In the 0-2 hour window, ultrasound-stimulated neurons displayed an increase in the mean frequency of evoked action potentials of 32% above control cell levels ($p = 0.023$). After 4-6 hours this increase was measured as 44% ($p = 0.0043$). By 12-14 hours this effect was eliminated and remained absent 24-26 hours post-stimulation. These changes to action potential firing occurred in conjunction with statistically significant differences between control and ultrasound-stimulated neurons in action potential half-width, depolarisation rate, and repolarisation rate, that were similarly eliminated by 24 hours following stimulation. These effects occurred in the absence of alterations to intrinsic membrane properties or synaptic ultrastructure.

Conclusion:
Stimulating neurons with 40 seconds of ultrasound enhances their excitability for up to 8 hours in conjunction with modifications to action potential kinetics. This occurs in the absence of major ultrastructural change or modification of intrinsic membrane properties. These results can inform the application of transcranial ultrasound in experimental and therapeutic settings.

Exploring the Correlation Between Polyglutamate (CAG) Repeat Length and Cognitive Decline in Huntington's Disease (HD)

Unique Code: TP001295

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Topic: Disorders, treatments and translational neuroscience

Introduction

HD is a progressive neurodegenerative disease, indicated by motor, psychiatric and cognitive symptoms. The extended CAG repeat on the Huntingtin (Htt) gene results in misfolding and aggregation of mutant Htt protein. It is well-known that motor symptom onset and severity correlate with CAG repeat length on the mutant gene and primary striatal pathology. Cognitive impairment often manifests fifteen years prior to motor diagnosis, but the relationship between cognitive symptom severity, CAG repeat length and extra-striatal pathology is not defined. Correlation between cognition and mutant gene structure would suggest a role for the mutant protein in neural circuit disruption and may provide novel early intervention opportunity.

Methods

Enroll-HD is a longitudinal global study containing data regarding profile, history and assessment of HD and control participants. A research proposal was accepted by Enroll-HD to gain data access. Data was included from core and extended cognitive tests (Verbal Fluency, Symbol Digit Modality, Stroop Colour, Word Reading and Interference, Trail-Making Test and Mini Mental State Examination (MMSE)).

Approach for Statistical Analysis

Generalised linear models with Poisson or binomial error were created in R to determine the role of CAG repeat length and age on test ability. Associated null models were created to obtain McFadden's R2 values and ANOVA testing.

Results and Conclusions

Cognitive decline inversely correlates with age and CAG repeat length in all cognitive tests. MMSE, Trail-Making Test B, Stroop Colour Naming and Interference Tests were highly sensitive to CAG repeat length and age. Suggested refinement of the Enroll-HD cognitive assessment battery to remove Verbal Fluency Test, Stroop Word Reading Test and Trail-Making Test A due to sensitivity or sophistication concern.

Inverse correlation between repeat length and cognitive performance implies that increased mutant protein affects cognitive neural circuits. These cognitive tests can be localised to specific brain regions; future work may use functional imaging to identify neural dysfunction in early HD when cognitive symptoms emerge to shift the focus of the field from late-stage striatal pathology and create novel therapeutic targets.

The Potential Role of a Polymorphic SVA in TMX2 in the Etiology of Neurodegenerative Disease

Unique Code: TP001298

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Topic: Disorders, treatments and translational neuroscience

Introduction

Thioredoxin-related Transmembrane protein2 (TMX2) participants in redox reactions which are vital for cell signalling and homeostasis. Two GWAS hits for schizophrenia have been identified in this locus and in linkage disequilibrium (r2=0.977, D'=1). Furthermore, a recent study has revealed that TMX2 could markedly impact on C9ORF72 toxicity, a gene which is a major genetic risk for amyotrophic lateral sclerosis (ALS) in addition to many other neurodegenerative conditions. This was of interest as its been demonstrated that ALS and schizophrenia have a 14% genetic overlap.

These schizophrenia GWAS hits were identified in a Han Chinese cohort, while C9ORF72 is not a major genetic risk for ALS in Chinese. We have therefore addressed genetic variation in a human specific SINE-VNTR-Alu (SVA) which contains the schizophrenia GWAS hit (rs7129727), and hypothesise this SVA could serve as a regulatory element in modifying TMX2 expression in both ALS and schizophrenia.

Methods

The human DNA samples were obtained from UK Motor Neuron Disease Association (MNDA). The frequency of the variants were determined by PCR.

Approach for statistical analysis

The Fisher's exact test was used.

Results and Conclusions

This SVA is located in TMX2 intron 1 and is 2,175bp in size, analysis demonstrated 3 elements in this SVA were polymorphic: the central 'variable number tandem repeat' (VNTR), the flanking hexamer repeat (CT element) and the poly A tail.

In our preliminary data from the MNDA cohort, 9 genotypes composed of 5 different alleles in the VNTR region of the SVA were identified among 990 samples (493 ALS vs 497 controls). 1 rare allele was only found in ALS patient with the allele frequency 0.1%. Genotype 1,3 and 2,5 were only found in ALS patients each with the frequency 0.2%. The alleles and genotypes of CT element and Poly A tail were also analysed but no significant difference was found between cases and controls.

Although the frequency for genetic association is low, the function of the SVA as a regulator of TMX2 will most likely be modulated by specific challenges in a cell specific manner. This could be one of the mechanisms by which the level of TMX2 in the cell is a modulator of both schizophrenia and ALS progression or severity.

Modification of hyaluronic acid for stereolithography 3D printing of hydrogel nerve conduits

Unique Code: TP001300

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Topic: Disorders, treatments and translational neuroscience

Introduction:
Peripheral nerve injuries (PNIs) arise from trauma or illness and can result in functional loss in that part of the body. Such injuries are reported in 15-40% of all trauma cases1.

Despite our extensive knowledge of the pathophysiology and regenerative mechanisms of PNIs, a therapeutic intervention capable of full functional recovery has yet to be developed.
Theoretically, nerve guidance conduits (NGC) can act as a bridge between two injured nerve ends, thus providing structural and trophic support for regenerating axons. Several of these conduits are under clinical investigation but few have made it to market.

Utilising a novel blend of biopolymers, polyethylene glycol dimethacrylate (PEGDMA) and hyaluronic acid (HLA), we hope to identify a suitable biomaterial for the 3D printing of NGC candidates.

Methods:
The effect of low molecular weight (LMW) (30-50kDa) HLA on neuronal (SH-SY5Y) and glial (RT4 D6P2T) cells was investigated using the MTT assay, resazaurin reduction (RR) assay and the trypan blue exclusion (TBE) assay. The results were then compared with HLA of increasing MW in order to select the optimal MW which allowed for neuronal and glial cell proliferation and attachment.

Statistical approach:
Statistical analysis was conducted using one-way and two-way ANOVA in Graphpad Prism with Tukey and Sidak's post-hoc tests respectively.

Results and conclusions:
LMW HLA did not induce cytotoxicity with the RR and the TBE assay. However, when assayed using MTT, significant toxicity in both cell lines was observed, with the SH-SY5Y appearing more susceptible. It was determined that this overestimation of cytotoxicity was due to enhanced cell detachment during MTT exposure in SH-SY5Y cells and not HLA-induced cell death, thus bringing into question the suitability of the MTT assay for SH-SY5Y experiments. Future experiments will focus on the modification of LMW HLA for incorporation into a NGC with novel biotherapeutics and PEGDMA.

References:
1. Gong H, Fei H, Xu Q, Gou M, Chen HH. 3D-engineered GelMA conduit filled with ECM promotes regeneration of peripheral nerve. J Biomed Mater Res. 2020 Mar;108(3):805–13.

Investigating lysosome dysfunction in a zebrafish model of lysosomal storage disorder, CLN2 disease

Unique Code: TP001301

Authors: Lisa Kiani - Comparative Biomedical Sciences Royal Veterinary College

Topic: Disorders, treatments and translational neuroscience

Lysosomal storage disorders (LSDs), a group of inherited genetic diseases, are often associated with early-onset neurodegeneration, highlighting the critical role of the lysosome in maintaining neuronal cell function and health. The study of LSDs can therefore generate insights into the interconnection between lysosomal dysfunction and neurodegeneration more broadly. Accumulating evidence from LSDs show that lysosome dysfunction can lead to impairment of autophagy, which is thought to contribute to disease pathogenesis. Here, we report on a model of CLN2 disease, an LSD caused by recessively inherited dysfunction of lysosomal serine protease Tripeptidyl Peptidase 1 (TPP1), leading to a characteristic accumulation of material in the lysosome. The mutant zebrafish larvae (tpp1-/-) show phenotypes that resemble the human disease, including neuronal and retinal degeneration, seizures and premature death (Mahmood et al., 2013). We show that this model is suitable to investigate the relationship of impaired autophagy and lysosomal dysfunction. Specifically, we developed novel transgenic lines with autophagosome and lysosome markers LC3 and Lamp1 respectively, tagged by ZsGreen fluorescent protein. Using these lines, we were able to reliably quantify lysosomal number, size and morphology, as well as autophagic flux in vivo. This initial dataset highlights severe lysosomal abnormality in tpp1-/- mutants, alongside blocked autophagic flux and alterations in autophagosome position. Furthermore, we show a perturbation in mTORC1 and TFEB signaling in tpp1-/- mutants. Thus, this model provides a high-content imaging-based strategy to investigate the perturbation of autophagic pathways, and to explore the therapeutic potential of modulating lysosome and autophagy function in CLN2 disease, with potential implications in other neurodegenerative diseases.

P2X7 receptor antagonism provides extended seizure-suppression in experimental temporal lobe epilepsy

Unique Code: TP001315

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Topic: Disorders, treatments and translational neuroscience

Introduction Epilepsy is a common brain disease characterized by spontaneous recurrent seizures (SRS). Frontline treatment is with anti-epileptic drugs. These have similar mechanisms of action, blocking neuronal ion channels and transmitter systems but fail to control seizures in 1:3 patients. P2X7 receptors (P2X7R) are ATP-gated ion channels mainly expressed by resting and reactive microglia. Upon activation, e.g. following tissue injury or prolonged neuronal excitation, P2X7Rs promote inflammation via release of interleukin-1β and modulation of neuronal function. Microgliosis has been reported to be sufficient for epileptogenesis and previous studies showed P2X7R antagonists have antiseizure effects in rodents. Here, we tested a potent and selective P2X7R antagonist (JNJ-54175446) in a mouse model of drug-resistant temporal lobe epilepsy. The findings suggest a potential disease-modifying treatment for epilepsy based on targeting the P2X7R.

Methods Adult male C57BL/6 mice (n=7/group) were subjected to status epilepticus (SE) by intra-amygdala

microinjection of kainic acid. Continuous EEG was performed using implanted telemetry. Two weeks after SE, when mice were displaying regular SRS, animals were assigned to either drug (JNJ-5417544; 30mg/kg) or vehicle (DMSO,10%; PEG E400) and received a single i.p. injection each day for 5 days, followed by a two-week washout. Digitized EEG recordings and SRS counts were analyzed offline using manual assessment and Labchart7.

Approach for statistical analyses Data were analyzed using ANOVA and Fisher's PLSD test or, for 2-group comparisons, Student's t test. Data are presented as mean ±SEM. Significance was accepted at $P<0.05$.

Results At baseline, vehicle mice displayed an average of 43.16 SRS compared to JNJ-54175446 treated group (36.16; $P>0.05$). During dosing with the P2X7R antagonist, seizure rates reduced (Veh; 43.5, JNJ, 19.16) but this did not reach significance ($P=0.34$). During washout after dosing, average SRS counts were significantly lower in JNJ-treated mice (Veh, 74.83; JNJ, 19.5).$p=0.0133$

Discussion This study shows that P2X7R antagonism attenuates SRS in a mouse model of drug-resistant epilepsy. Antagonists of the P2X7R may represent novel targets for treatment of drug-resistant epilepsy in patients.

GABAergic modulation of cortical network oscillations underlying motor learning in frontotemporal lobar degeneration

Unique Code: TP001318

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Topic: Disorders, treatments and translational neuroscience

Background: Patients with frontotemporal lobar degeneration (FTLD) are typically impulsive and disinhibited and show perseverative behaviours. This indicates an impaired ability to adapt and update behaviours in response to changing environmental cues. These abnormal behaviours are linked to prefrontal atrophy, loss of GABAergic neurotransmission, and reduced neurophysiological activity.

Method: We used magnetoencephalography to test the hypothesis that that FTLD impairs cortical oscillations which, like behaviour, adapt slowly over trials. We associate these impairments with loss of GABAergic neurotransmission. We used the GABA re-uptake inhibitor Tiagabine in a double-blind placebo controlled design, including 11 people with behavioural-variant frontotemporal dementia (bvFTD), 11 people with progressive supranuclear palsy (PSP) and 18 healthy controls. In a novel visuomotor task participants were requested to move a cursor with variable speeds into a target box. Time-frequency per trial was used to generate power spectra. Linear mixed models examined behavioural performance and oscillatory power over trials, to estimate learning over time. Significant power differences were source-localised using LCMV beamformer.

Results: Although patients could complete the task, their performance was impaired relative to controls, with slower learning over trials. Cortical oscillations, associated with movement, learning and accuracy, were diminished in the

patient groups. Tiagabine improved the learning slope in patients but had differential effects on the oscillations related to accuracy and trial number as a function of the FTLD diagnosis: in bvFTD Tiagabine reduced beta desynchronisation while in PSP Tiagabine enhanced it. The Beamformer localised these effects to prefrontal, premotor and motor cortices, revealing that the right prefrontal cortex is a key site of drug interaction.

Conclusion: Dysfunctional behavioural and oscillatory dynamics in bvFTD and PSP can be modified by GABAergic intervention. We interpret the differential response to Tiagabine as a function of baseline differences in atrophy and physiology between the patient groups, and predict a differential effect of Tiagabine according to GABA concentration.

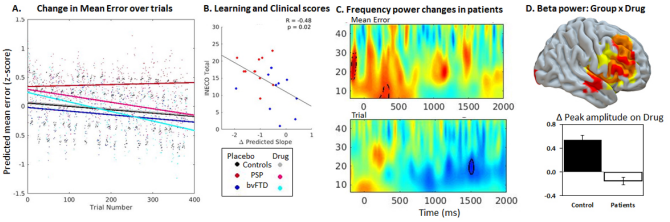

Figure A) Linear mixed model results showing reduction of mean error over trials, with significant improvement on drug for patients.
B) Changes in learning on drug were greater for patients with higher scores on the INECO frontal screening.
C) Differential effects of drug on frequency power in patients in relation to mean error (top) and change over trials (bottom) showing an increase in early alpha/beta for bvFTD and a later enhancement of Beta desynchronization for PSP.
D) The interaction of drug on beta power was localised to right prefrontal regions, revealing a greater desynchronization in patient groups compared to controls, peak difference at [32 28 14] shown in plot.

Who's in control? The influence of locus of control (LOC) upon psychosocial aspects of living with multiple sclerosis

Unique Code: TP001352

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Topic: Disorders, treatments and translational neuroscience

Background: Multiple sclerosis (MS) is a neurodegenerative disease whose burden is in part due to psychosocial symptoms. The impact of an individual's locus of control (Internal, Powerful Others or Chance) upon psychosocial aspects of their condition has been explored previously, but no conclusive evidence has yet been presented.

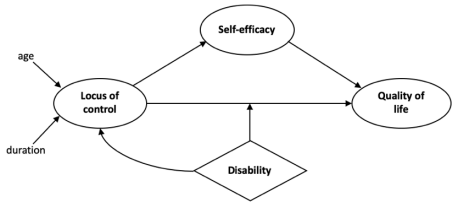
Objective: To determine the influence of locus of control (LOC) upon psychosocial aspects associated with MS, and whether subtype and severity of MS differentiate LOC.

Methods: 5059 participants with MS completed a questionnaire pack as part of the ongoing Trajectories of Outcome in Neurological Conditions (TONiC) study. The pack included the Multidimensional Health Locus of Control Scale, together with a range of other scales measuring disability, quality of life (QOL) and other psychosocial aspects. Associations between LOC and sociodemographic (age, gender, and level of education) and clinical variables (disease duration, disability, depression, anxiety, self-efficacy, and QOL), were tested using ANOVA analyses and chi-squared tests.

Results: Different aspects of LOC were found to be significantly associated with all of the clinical variables tested and

age, but not gender or level of education. Internal (ILOC) and Chance LOC (CLOC) were associated with higher self-efficacy and QOL than Powerful Others LOC (PLOC); however, in individuals with very high levels of disability, ILOC was associated with lower QOL, together with higher depression. The proportion with ILOC was significantly lower in those with secondary progressive MS (SPMS) compared to relapsing-remitting MS (RRMS).

Discussion: In MS, belief in powerful others to control one's disease rather than belief in one's self or chance, is associated with lower self-efficacy and QOL. The observed shift away from internality of LOC with MS progression may not be maladaptive, but rather a protective adaptation to reduce psychological distress.



Mediating effect of self-efficacy on the LOC-QOL relationship in MS. Locus of control (LOC) influences quality of life (QOL) through self-efficacy (SE), but not through variables such as depression and anxiety. The LOC-SE-QOL relationship is not moderated by disability. However, the LOC-QOL relationship does change with very high disability, independent of SE. Age, disease duration and disability are all associated with LOC.

Virally-mediated Synaptic Dysfunction in ALS

Unique Code: TP001357

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Topic: Disorders, treatments and translational neuroscience

Introduction

Amyotrophic lateral sclerosis (ALS) is a universally fatal neurodegenerative disorder of the body's motor system. Unfortunately, there is no cure for ALS. The goal of the present study is to identify whether the interaction between the Human Endogenous Retrovirus type K (HERV-K) envelope (env) protein and neuronal synapses could serve as a basis for new therapeutic approaches for ALS. HERV-K is an element found in the human genome but not actively expressed in healthy adults. However, one-third of ALS patients seen at the National Institutes of Health have evidence of active transcription of HERV-K RNAs, including HERV-K env RNAs.

Methods

Bulk human RNA sequencing data available through the New York Genome Center (NYGC) ALS Consortium was utilized. Data was analyzed using Qiagen Ingenuity Pathway Analysis (IPA) and previously published methods (Johnson et al. 2015).

A transgenic mouse model of ALS in which the HERV-K env protein is expressed was used to examine synapses directly (Li et al. 2015). This was accomplished using both structured illumination microscopy (SIM) and electron microscopy (EM) on mouse brain sections. For EM, synapses were identified based on morphology. For SIM, synapses were identified by labelling for both Synaptotagmin1 (pre-synaptic) and Homer1 (post-synaptic) elements.

Approaches for statistical analyses

For the RNA sequencing data, z and p values of pathway enrichment (IPA) as well as Welch modified t-test were used to determine significance. For the quantification of synapses, a Student's t-test was used to determine significance.

Results and conclusion
Significant changes were observed in genes involved in axon guidance and cAMP-response element binding protein (CREB) signaling in the motor cortex. This was in contrast to changes in expression of inhibitory synaptic and synaptic plasticity genes in the frontal cortex. Preliminary EM and SIM data suggest an increase in synapse number in the motor cortex of transgenic compared to wildtype animals in the motor cortex. These results highlight the important role of synapses in ALS pathophysiology.

References
Johnson, K., et al. (2015). PLoS One, 10(4).
Li, W., et al. (2015). Science Translational Medicine, 7(307).

"Feeling Run Down": Links Between Inflammation and Disrupted Reward Processing in Depression

Unique Code: TP001360
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Topic: Disorders, treatments and translational neuroscience

Introduction: One of the core symptoms of Major Depressive Disorder (MDD) is motivational anhedonia, the lack of pleasure-seeking behaviour, biologically conceptualised as a deficit in reward processing. Inflammation is one of the key proposed mechanisms linked to MDD. Given the overlap between some somatic features of chronic inflammation and depression (particularly decreased motivation), we sought to investigate the relationship between inflammation and reward processing in depression.

Methods: We analysed data from a subset of Generation Scotland participants (N = 1,171) with a range of depressive symptoms. Inflammation was derived from acute serum-based C-Reactive Protein (CRP) and chronic measures of CRP exposure through DNA methylation data (Green et al., 2020). Reward processing deficits were derived from an adapted Cambridge Gambling Task (CGT) and an fMRI reward value task (Romaniuk et al., 2019). We hypothesised that increased inflammation would be associated with disrupted reward processing.

Approach for Statistical Analysis: Power analysis was performed in G*Power. All other statistical analyses were performed in R. We tested associations between inflammation markers and behavioural measures of reward processing using univariate generalised linear mixed models with FDR correction, with age, sex, BMI, and study site as covariates. In our exploratory analyses, we tested interactions of alcohol use, smoking, and lifetime history of MDD in these regression models.

Results and Conclusions: We found no statistically significant associations between inflammation markers and measures of reward processing ($p > 0.05$). In our exploratory analyses, we found that recent alcohol use influenced the effects of serum CRP elevation on some measures of reward processing with moderate effect sizes. Crucially, we also found that the effects of DNAm CRP elevation on CGT performance, and the effects of serum CRP elevation on brain activation on the fMRI reward task (particularly in the amygdala), were influenced by a lifetime history of MDD with moderate-to-large effect sizes. Therefore, our findings suggest that systemic inflammation may be involved in disrupted reward processing in MDD, thus offering a potential biological process underlying key symptoms of depress

Exploring the 5-HT4 agonist, prucalopride, as a potential pro-cognitive agent in the human brain

Unique Code: TP001373

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Topic: Disorders, treatments and translational neuroscience

Introduction: Cognitive deficits within psychiatric disorders are common, under-recognised, and difficult to treat. Animal studies suggest that 5-HT4 receptor stimulation enhances cognition likely due to acetylcholine and BDNF release. We aimed to provide the first exploration of short-term prucalopride (a partial 5-HT4 agonist) on human behavioural and neural memory processing. We hypothesised that prucalopride would improve episodic memory and increase activation of hippocampal neural networks during an fMRI task.

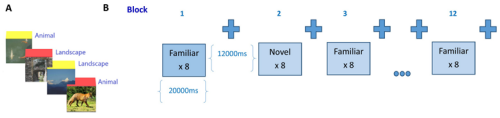
Methods: Right-handed healthy participants (N=44, 18-36) were administered prucalopride (7 days x 1mg) or placebo, in a double-blind, randomised, experimental medicine design. On day 6, participants underwent a 3T scan including an fMRI memory task designed to induce hippocampal activation (Figure 1). After the scan, ability to separate novel, familiar, and 27 additional “distractor” images was tested.

Approach for statistical analyses:
Behavioural data were analysed using repeated-measures ANOVA. Imaging data were analysed with FSL, correcting for multiple comparisons, perfusion, and grey matter maps. Brain activations showing significant group differences were identified using cluster-based thresholding ($Z>3.1$, $p<0.05$ corrected). We pre-specified regions of interest analyses.

Results and conclusions: 5-HT4 agonism improved recognition of previously-seen images compared to placebo (novel+familiar versus distractors) ($F(1,38)=5.18$, $p=0.029$), and increased accuracy to distinguish each image category (novel/familiar/distractor) ($F(1,38)=4.806$, $p=0.035$). Prucalopride also led to greater activation in the hippocampus bilaterally during processing scenes [$F(1,42)=5.19$, $p=0.028$, $\eta p2=0.11$]. On whole-brain fMRI analysis, prucalopride increased activation in the right angular gyrus (familiar mean, prucalopride>placebo, $Z=4.1$, $p<0.005$, peak voxel:x=42,y=-60,z=60, cluster size=168 voxels).

We found 6 days of prucalopride led to improved cognitive performance. Following memory encoding, 5-HT4 agonism also increased activation to the hippocampus and a linked memory-processing region. Our findings support 5-HT4

agonists as human pro-cognitive agents, with the potential to aid patients with cognitive impairment secondary to psychiatric disorders.



The memory encoding task design

(A) Before the fMRI scan, 8 "familiar" pictures (4 animals, 4 landscapes) were presented 8 times pseudorandomly on a computer screen. Using a 2-button response, participants classified these as animal / non-animal.

(B) During the fMRI scan, images were presented in 6 familiar and 6 novel blocks: image presentation 2000 ms, inter-stimulus interval 500 ms, block duration 20000 ms. There was 12000 ms of rest (fixation cross) between each block of images. Using a 2-button response, participants classified these as animal / non-animal.

Intraoperative mapping of cognitive control regions in the frontal cortex using electrocorticography

Unique Code: TP001382

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Topic: Disorders, treatments and translational neuroscience

Introduction

Intraoperative mapping during awake neurosurgery guides the resection of brain tumors to minimize the loss of healthy tissue and preserve brain function. Mapping is commonly used for language and motor functions. Cognitive control, referring to the processes underlying flexible and goal-directed behavior, is challenging to map intraoperatively. It is thought to be supported by a frontoparietal network (FPN), co-activated by increased task difficulty across many cognitive domains. Here we aim to identify an electrophysiological signature related to cognitive control as converging evidence with fMRI data and as a first step towards its potential use for intraoperative mapping.

Methods

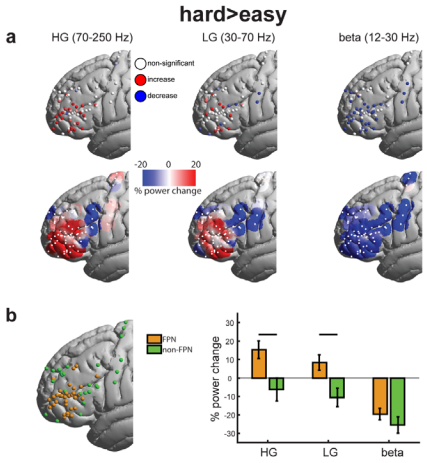
We recorded electrophysiological activity from 79 electrodes placed on the lateral frontal cortex in 13 patients undergoing awake craniotomy for tumor resection. During surgery, patients performed 2 tasks with difficulty level manipulation, repeated 3-4 times each: counting 1 to 20 (easy) and alternate counting of numbers and alphabets (1, a, 2, b, up to 20; hard).

Approach for statistical analysis

For each electrode, a permutation testing approach was used to statistically compare power across conditions. Trials from both conditions were concatenated to form a loop. Trial markers were “rotated” along the loop using a random jitter and we computed the mean power (for each condition) and power ratio (across conditions) based on the new trial markers. This was repeated 100,000 times to create a surrogate distribution against which statistical significance was calculated. T-test was used to compare power between groups of electrodes.

Results and conclusions

By contrasting hard vs easy demands, spectral analysis revealed a localized frontal region with power increases in the gamma range (>30 Hz). This contrasted with spatially distributed power decreases in the beta range (12-30 Hz) (Fig a). Furthermore, electrodes that overlapped with a canonical FPN mask showed significant increases in gamma power compared to those outside of FPN (Fig b, line $p<0.05$). Thus, using similar task difficulty manipulations, electrophysiology and fMRI signals converged on localizing frontal regions related to cognitive control and support their potential for intraoperative mapping.



A Placebo Controlled, Double Blind, Randomised Study Of Low-dose Zolpidem For The Treatment Of Motor Deficits In Late-stage Parkinson’s Disease

Unique Code: TP001398

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Topic: Disorders, treatments and translational neuroscience

INTRODUCTION

Parkinson’s is characterised by akinesia, bradykinesia, and rigidity. The standard treatment is dopamine replacement therapy. However, this progressively becomes ineffective leading to wearing off effects such as freezing and dyskinesias. Therefore, there is a real need for alternative non-dopaminergic treatments to maintain quality of life. Zolpidem (ZP), usually prescribed for insomnia, acts at the GABA-A receptor. Currently, there are over 40 reports on the benefit of ZP in a variety of movement disorders. Here, we present initial results from Clinical Trial EudraCT:2017-004297-34.

METHODS
28 patients were recruited (12M and 16F), of age 45-78 years (67.25±1.54) with a Hoehn & Yahr score ≥2.5. The primary outcome was motor function as measured by UPDRS III. Patients were administered either ZP (5mg) or placebo and the assessments were repeated one hour later.

STATISTICS
The analysis included paired T-tests (before and after drug administration) and independent T-tests (between ZP and placebo). Spearman's Rho test was used for correlation analysis. All statistics are presented as mean ± SEM.

RESULTS AND CONCLUSION
No serious adverse effects or falls were reported, and adverse effects were transient. Significant symptomatic improvements were observed following administration of ZP (UPDRS III -7.2±2.37, $p<0.0001$) and placebo (-8.43±2.03, $p<0.0001$). However, correlation analysis showed that with ZP the greatest reductions were found in those patients who had exhibited the greatest deficits. Thus, the reduction in UPDRS III was significantly correlated, not only with initial total UPDRS ($p<0.001$) but also with initial UPDRS III ($p<0.01$). With placebo, no significant correlations were found. Analysis of individual symptoms confirmed ZP caused a significant reduction in action/posture tremor (-1.14±0.35, $p<0.01$), upper limb rigidity (-1.43±0.36, $p<0.01$), lower limb rigidity (-1.43±0.42, $p<0.01$), and hand movements (-0.93±0.35, $p<0.05$). The significant beneficial effects of ZP on action/posture tremor and hand movements were not observed on the administration of placebo.

This study adds weight to the increasing body of evidence indicating that low-dose ZP provides clinically relevant benefits without major side-effects.

Whole brain imaging to investigate cFos activation in a rodent model of autism spectrum disorders

Unique Code: TP001401

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Topic: Disorders, treatments and translational neuroscience

Autism spectrum disorders (ASD) are characterized by social impairments and restricted behaviours. To investigate how changes in brain activation mediate behaviour, rodent models of ASD, such as Fragile-X knockout (Fmr1-/y), are a powerful tool. Previous studies using this model have provided valuable insights into functional differences between neuronal types, however studies are generally constrained to a single brain region of interest. As a result, whole brain changes in neuronal activity in ASD are largely unknown. To identify neurons in the rat brain that are activated during behavior, we used the immediate-early gene cFos as a proxy for neuronal activation and combined this with optical clearing and light-sheet microscopy1. Given amygdala-dependent emotional processing is known to be altered in individuals with FXS, we hypothesised that cFos expression in the Fmr1-/y rat brain is altered compared to wild type

(WT) in response to fear conditioning. We compared WT and Fmr1-/y rats that underwent a fear conditioning paradigm. Animals received a conditioned (CS: light) paired with an unconditioned stimulus (US: foot shock; paired group), and were compared with animals that received only the CS, or that remained home-caged (naive). Brain tissue was obtained, immunolabeled against cFos, cleared with iDISCO1 and imaged in a Ultramicroscope II. We established a pipeline for automatic cell quantification in a custom-made atlas of the amygdala that delineates the basolateral complex (BLA; made up of lateral:LA, basal:BA and basomedial:BM) and the central nucleus (CeA)2. Our analysis showed an increase in cell density of cFos+ neurons in the BA and BM nuclei of WT and Fmr1-/y rats in the paired group, compared with naive rats. This increase was also observed in WT-CS only, but not Fmr1-/y -CS only group. Finally, no cell density changes were observed the LA or CeA nuclei of WT or Fmr1-/y rats (One-way ANOVA, Tukey post-hoc test). Our approach to detect neuronal activation in response to different stimuli enabled us to detect changes in cFos-expression in the Fmr1-/y rat. In particular, the deficit observed in the CS only group suggests a reduction in responsiveness of the BLA to ongoing sensory events. 1.Renier,N.Cell 2014. 2.Janak,P.H.&Tye,K.M. Nature 2015.

Internal states and homeostasis

A hunger-sensitive hippocampal circuit regulates the decision to eat

Unique Code: TP001034

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Topic: Internal states and homeostasis

Feeding behaviour is a complex motivated behaviour that requires organisms to integrate features of the environment and internal states, such as hunger, in deliberating over the decision to eat. The hippocampus – a brain region that supports spatial cognition and episodic memory – is increasingly recognised to contribute to such decision-making processes. However, it remains unclear whether the hippocampus regulates the decision to eat during free behaviour. To address this question, we used in vivo calcium imaging during free feeding behaviour in mice to monitor the neural activity of the ventral subiculum (vS) – one of the main output structures of the ventral hippocampus. Where appropriate, data were analysed using paired and unpaired t-tests, one- and two-way analysis of variance and multiple linear regression. Using these methods, we found that vS activity encoded the investigative approach phase of feeding behaviour (multiple linear regression, beta = 0.48±0.16, one-sample t-test, $p = 0.02$) and that activity during this period negatively correlated with the probability of transitioning from food investigation to consumption (Pearson correlation, $r = -0.7$, $p = 0.01$). Furthermore, the sensitivity of vS to the hunger state could be mapped to vS neurons projecting to the nucleus accumbens (vS-NAc) as opposed to the lateral hypothalamus (vS-LH). Ghrelin – a hormone signalling the hunger state – modulated inhibitory synaptic transmission specifically in vS-NAc neurons (synaptic current amplitude between vS-NAc and vS-LH, unpaired t-test, $p = 0.004$). Consequently, reducing ghrelin signalling in vS-NAc neurons through RNA interference (RNAi)-mediated molecular knockdown and artificially elevating vS-NAc activity through optogenetics were sufficient to shift the feeding strategy of animals, effectively curtailing overall food consumption. Taken together, these results provide evidence for a hunger-sensitive hippocampal circuit that exerts control over the decision to eat.

Effects of hunger state on protein expression and CREB phosphorylation in the nervous system of Lymnaea stagnalis

Unique Code: TP001293

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Topic: Internal states and homeostasis

Introduction: Hunger state can crucially influence an animal's drive to search for food or learn appetitive associations. However, the molecular basis of this influence is not well-understood. Here we used an established model animal in learning and memory research, Lymnaea stagnalis, to further our understanding of the effect of hunger state on the expression and phosphorylation of proteins in the brain. Combined with our detailed knowledge on how hunger state influences feeding behaviour and underlying circuits, this work has the potential to provide significant contribution to the discovery of target molecules for memory improvement.

Aims: To compare protein expression and CREB phosphorylation in the brain of food-deprived and satiated animals.

Methods: Desalted tryptic peptides of brain lysates from food-deprived and satiated animals were separated by nano liquid chromatography and analysed by tandem mass spectrometry. Furthermore, we analysed the expression and phosphorylation of Cyclic AMP Response Element-Binding protein (CREB) transcription factors, which are important in appetitive learning, by western blotting.

Approach for statistical analysis: Statistical comparisons were made with Kruskal-Wallis one-way ANOVA analysis or Unpaired two-tailed Student's t-test with Welch' correction by using GraphPad Prism 6 or Perseus.

Results: In food-deprived and satiated animals, we found differentially expressed proteins in the pathways of energy metabolism, glycolysis and citrate cycle. We also found that proteins involved in translation were decreased significantly in food-deprivation and increased in satiety. There were significant changes in the expression of certain neuropeptides that are involved in signal transduction. Although there were no significant hunger-state dependent differences in the expression of total or phosphorylated CREB1 or total CREB2, the variance of CREB1 and CREB2 data was significantly greater in the satiated versus the food-deprived animals.

Conclusions: Our mass spectrometry analysis revealed possible molecular links between hunger state and memory formation. Notably, the variance of both CREB1 and CREB2 expression was increased by satiety.

Methods and technology development

Now you see it, now you don't: optimal parameters for interslice stimulation in concurrent TMS-fMRI

Unique Code: TP001041

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Topic: Methods and technology development

Concurrent TMS-fMRI is an inferentially powerful technique used to examine causal relationships between brain activity and behaviour. Despite its increasing popularity, TMS-fMRI remains technically challenging. In particular, TMS pulses cause large artifacts in the fMRI image. These artifacts can be removed by interpolating over affected slices (e.g., Jackson et al. 2020), or by timing TMS delivery to avoid slice read out. For example, de Lara et al. (2017) applied TMS during a delay introduced at the end of each fMRI volume (TR). This avoids artifacts but reduces temporal resolution and experimental flexibility. Here we examined the feasibility of a third approach, applying TMS during short gaps between fMRI slices. We quantified signal dropout and changes in temporal signal-to-noise ratio (tSNR) for TMS pulses presented at timepoints from 100ms before to 100ms after slice onset. We delivered TMS at 20%, 60%, or 100% of a MagPro XP stimulator output, using MagVenture's MR-compatible TMS coil, and sent 1, 2 or 3 pulses per volume. We used a circular phantom, two 7-channel TMS-dedicated surface coils (de Lara et al., 2015), and a multiband sequence (factor=2) with interslice gaps of 100ms and 40ms, on a Siemens 3T Prisma-fit MRI scanner. For each voxel, tSNR was defined as the average signal over its standard deviation through time. Dropout was quantified as the root mean square deviation (RMSD) across voxels in a slice, compared to a mean reference image with no-TMS, and expressed as a percentage of the total possible dropout for each slice (following de Lara et al., 2017). We found that, even at 100% stimulator output, pulses applied a minimum of 40ms before, and 50ms after, the onset of slice readout, avoid incurring artifacts (Figure 1). Despite an increase in dropout associated with trains relative to single pulses, these trains did not affect the signal if presented outside the critical window (-40ms/+50ms from slice onset). Thus, an inter-slice TMS protocol can be achieved for single pulses of trains with a frequency of up to ~10 Hz, using a multiband sequence with a slice acquisition time of 60ms and interslice gap of 40ms. Faster stimulation frequencies would require shorter slice acquisition times, for example using in-plane acceleration.

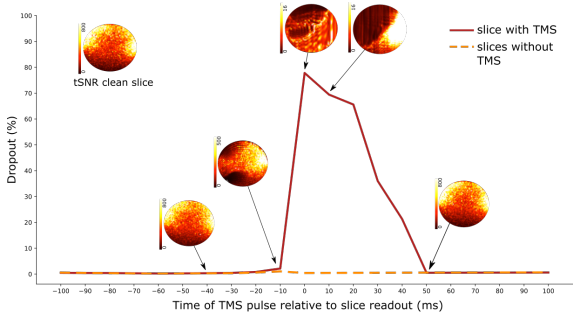

Figure 1. Dropout and tSNR: Figure 1 depicts the dropout (%) of a slice where a single TMS pulse was applied at 100ms pre- to 100ms post-slice onset (red line), compared to slices with no TMS applied (orange line), where 100% dropout indicates that no signal was acquired. Sample tSNR maps are also depicted to illustrate the corresponding change in tSNR at key pulse timings (colour bars indicate the range of tSNR. Note that the range varies between maps). These data indicate that the dropout and tSNR is indistinguishable from baseline before -40ms and after +50ms relative to slice readout.

NORMAN: Automated novel object recognition test using artificial neural networks

Unique Code: TP001118

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Topic: Methods and technology development

Background: The novel object recognition test (NORT) is widely used in Neuroscience research as a quantitative measure of memory in rodent models. Memory is assessed by comparing the exploration time of novel and familiar objects. These times are summarised in a discrimination index (DI) calculation, forming the quantitative output of the test. The current data extraction method for this test is very laborious, time consuming, and prone to inter and intra-experimenter variation. An automated NORT data extraction method will allow for reproducible, high-throughput analysis of rodent models of memory and reduce the number of animals needed in experiments. I developed a system to automate data extraction and analysis for the NORT from video.

Methods: The methodology developed used the DeepLabCut™ neural network package to track relevant features of mice in a novel object recognition task. I developed an object detection algorithm, alongside angle and proximity calculations in order to extract the relative position of the mouse to both objects in the test. I created a new neural network named Novel Object Recognition Mouse Analysis Network (NORMAN) and trained it using previous experienced human scoring of the NORT. I then evaluated the system by comparing the output of NORMAN on unseen NORT videos to the performance of an experienced human scorer using DIs. The DI calculation was time with novel object minus time with familiar object, divided by the time with both objects.

Results: The DIs calculated with NORMAN were compared with human calculated DIs using a KS test (n=60). The D score was 0.083, with a p-value of 0.986. This shows the DI distributions of human and NORMAN results are statistically similar. NORMAN achieved an average accuracy per-frame (every 55 milliseconds) of 81%.

Discussion: The NORMAN system provided biologically relevant, accurate results for the NORT. The NORMAN system can process 5-minutes of video and Deeplabcut™ pose information in under 10 seconds, representing a large time save for experimenters.

Quantitative spatial analysis of 100 genes to study the effect of amyloid pathology in Alzheimer's Disease (AD)

Unique Code: TP001145

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Topic: Methods and technology development

Although clear hallmarks such as Aβ plaques and neurofibrillary tau tangles are key pathological events in AD, we still do not fully understand the disease at the cellular level. We have little understanding of why only some cells and brain regions are more vulnerable to pathology, and the molecular changes cells undergo as the pathology sets in.

Single-cell RNA sequencing studies do shed light on the molecular changes at the cellular level. However, single-cell RNA sequencing studies lack the spatial context. Investigations of the transcriptomics changes that take place at the vicinity of the pathology (i.e. spatial resolution) will potentially give a better understanding of cause and effect relationships during disease progression.

Here, we employ a new highly sensitive imaging-based in situ transcriptomics technology to detect and quantify the expression of 100 genes in an AD mouse model (APP/PS1). We chose 100 genes that are associated with the following signaling pathways: disease-associated-microglia (DAM), inflammasome, WNT-signaling, and the complement. We present a quantitative analysis of changes in these 100 genes as a function of distance from Aβ plaques. We confirm enrichment of cst7 (log foldchange: 1.2) in the vicinity of the plaques. Cst7 can be linked to clusters of DAM that were detected near plaques based on the transcript signature of individual segmented cells and overall enrichment of markers in the periphery of plaques. Statistical significance of marker enrichment is assessed via T test. APP/PS1 tissue showed a marked reduction in WNT-signaling throughout the affected tissue independent of cortical layers and associated cell types.

We demonstrate that the Aβ plaques have a concerted effect on different signaling pathways and cell types in close vicinity of the pathology.

Cytoarchitectonic maps help explain patterns in resting state fMRI signal

Unique Code: TP001166

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Topic: Methods and technology development

Introduction: Resting state functional Magnetic Resonance Imaging (RS-fMRI) measures neuronal activity. One of the most used methods to analyze RS-fMRI signal is the Probabilistic Independent Component Analysis (PICA). The PICA allows to depict brain functional connectivity (FC) networks. Yet most of the PICA output maps are classified as artifacts or noise of an unknown source. We hypothesized that these unexplained RS-fMRI signal patterns can be linked to oxygen metabolism and/or blood flow in cortical layers. This study aimed at (i) providing preliminary evidence to the effects of laminar organization of neocortex on RS-fMRI signal, and (ii) evaluating the application of laminar maps to aid the classification of IC maps.

Methods: RS-fMRI data from 54 healthy adults (age M=43, SD=12 years; 100% males) were preprocessed using a standard pipeline. These data were then used to (1) generate 20 IC maps with the PICA; and (2) extract RS-fMRI signal intensity from 21 predefined Brodmann's (BA) brain regions that show extreme variation in the relative thickness of cortical layers IV and VI. The 21 predefined BA regions were classified into laminar maps 1-4 based on their

cytoarchitecture.

Approach for statistical analysis: Pearson's correlation coefficient examined the relationship between the relative thickness of the cortical layers and the RS-fMRI signal properties. Variables included: (a) the binary values for the relative cortical thickness (i.e., 0=lacking/thin vs. 1=massive) of layers IV and VI; and (b) the standardized RS-fMRI signal intensity values (i.e., mean, standard deviation and variance) that were averaged at a within-individual level across the voxels of each BA region.

Results and conclusions: We found that RS-fMRI signal is significantly related to the relative thickness of the cortical layer VI but not layer IV. The laminar maps 1–4 overlap with four separate IC maps (Fig 1). Thus, the laminar maps 1–4 improve classification and interpretation of the IC maps. Moreover, the laminar maps 1–4 may be considered as FC networks that are the bridging piece between particular cognitive functions. Together, these data provide preliminary evidence to the fundamental questions about the role of cortical layering in RS-fMRI signal and brain FC networks.

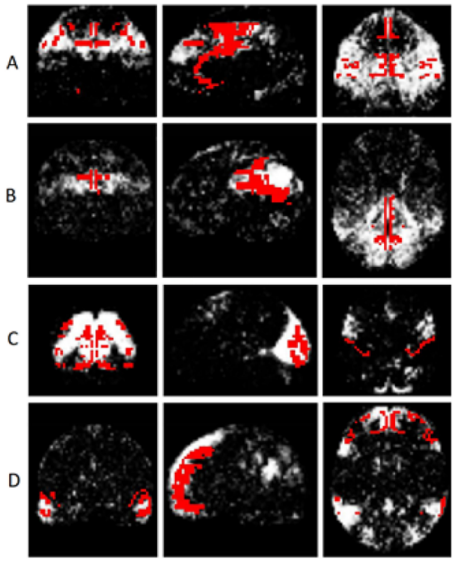

Figure 1. Overlap between the IC maps and laminar maps: row A – IC 20 with red blobs representing laminar map 1; B – IC 8 and laminar map 2; C – IC 17 and laminar map 3; D – IC 5 and laminar map 4. For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article: Egbert, A.R., Lojek, E., Biswal, B., Pluta, A., and Harmonia Group. (2021). The laminar pattern of resting state in human cerebral cortex. *Magnetic Resonance Imaging*, 76:8-16. https://doi.org/10.1016/j.mri.2020.10.013.

Development of a 3D human induced pluripotent stem cell spinal cord scaffold system to investigate and promote spinal cord repair

Unique Code: TP001225

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Topic: Methods and technology development

Following spinal cord injury, trophic astrocytes become 'reactive' and contribute to scar formation, preventing injured neurons from regrowing their axons through the lesion site to restore sensorimotor function. Currently, no full therapeutic exists to facilitate cord repair due to the poor understanding of the underlying cellular mechanisms post-injury and the lack of supportive environment to promote recovery. Building on expertise in developing peripheral nerve guidance scaffolds we aimed to create a biomimetic tissue scaffold for 3D spinal cord modelling of neurons and glial cells and at the same time provide a trophic implant capable of bridging the injury site for repair. Screening of native central nervous system (CNS) extracellular matrix (ECM) proteins revealed that collagen-IV and fibronectin combined, enhanced motorneuron (39%, $p<0.01$) and spinal cord astrocyte outgrowth (70%, $p<0.05$). Collagen-IV and fibronectin also increased astrocyte process number ($p<0.05$), metabolic activity ($p<0.05$) and decreased levels of reactivity ($p<0.05$). Subsequently hyaluronic acid scaffolds with mechanical properties and aligned microarchitecture mimicking the spinal cord, functionalized with collagen-IV and fibronectin, were seeded with induced pluripotent stem cell (iPSC)-derived astrocytes and neurons. We showed that soft scaffolds (0.9kPa) promoted cell viability ($p<0.05$), outgrowth/infiltration ($p<0.0001$) and differentiation compared to stiffer scaffolds (3kPa & 6.1kPa). Furthermore, soft scaffolds encouraged growth of iPSC derived sphereoids that subsequently formed extensive neuronal/astrocytic networks with distinct beta-tubulin III+ (neurons) and GFAP+ (astrocytes) processes that connected with other spheroids. Here we show that a novel scaffold system with physiochemical and mechanical properties matching that of the uninjured spinal cord supports robust iPSC derived astrocytic and neuronal growth. These findings have implications for 3D modelling of astrocyte-neuronal interactions in an anatomically and physiologically relevant environment and for further development of scaffold therapeutics for promoting cord repair. Research funded by the Anatomical Society UK, IRFU Charitable Trust and SFI-AMBER Centre.

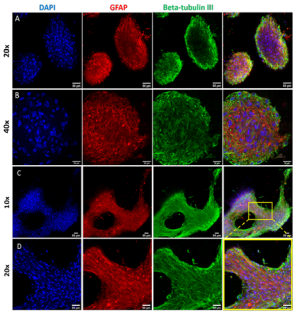


Figure 1. iPS cells in HyA scaffolds can form multicellular structures. iPS cells seeded in HyA scaffolds form multicellular spherical structures where neurons are localised to the exterior (A&B). In soft 3mg/mL scaffolds, cellular networks are capable of forming between cell clusters (C&D). All Scale bars = 50µm.

Spatio-temporal mapping of 3R and 4R Tau isoforms during mouse brain development using BaseScopeTM in situ hybridization technology

Unique Code: TP001236

Authors: Claudia Tamburini - Technical Services Bio-Techne,

Topic: Methods and technology development

The microtubule-associated protein tau (MAPT) gene encodes a multifunctional protein that is predominantly expressed in neurons where it has a role in microtubule assembly and stability, axonal transport and neurite outgrowth. Neurodegenerative diseases such as Alzheimer's disease are a result of toxic tau aggregates often referred to as tauopathies. Alternative splicing of exon 10 that encodes for the microtubule-binding repeat sequence gives rise to two protein isoforms with either three or four microtubule-binding repeats, in the 3R Tau (exon 10 exclusion) and 4R Tau (exon 10 inclusion) variants, respectively. The expression of both isoforms is developmentally regulated, with each of

these isoforms likely to have distinct physiological roles. The balance between both isoforms (3R:4R ratio) is known to be different in normal and diseased brains.

There is a critical need to map the spatial and temporal expression patterns of Tau isoforms at a single-cell resolution during brain development and disease progression, to elucidate the regulatory mechanisms and function of Tau isoforms.

Here we report the development of an in situ hybridization (ISH) assay for the isoform-specific detection of 3R and 4R Tau mRNA and their profiles during mouse brain development.

The BaseScope ISH technology was employed in this study to detect the alternative splicing of MAPT exon 10 at the single cell level, with probes targeting the junction between exon 9 and 10 junction (specific to isoform 4R) and the junction between exon 9 and 11 (specific to isoform 3R). These probes were validated on transfected cells, then used to evaluate the neuroanatomic expression of 3R and 4R Tau variants during mouse brain development in postnatal ages P1, P10, P30, and P56 of adult C57Bl/6J mouse. An ISH/IHC dual assay was also used to combine the probe signal with NeuN staining.

Our results revealed a clear opposing dynamic between the 3R and 4R isoforms over the course of development in the cortex and hippocampus. To conclude, the unique BaseScope probe designs used in this study provide a powerful approach to study the spatial and temporal expression patterns of the different Tau splice variants, with single-cell resolution in animal and cell-based models.

High-throughput spatial mapping of diverse gene signatures & cell type specific markers in mouse brain using a multiplexed in situ hybridization assay

Unique Code: TP001246
Authors: Sara Wrobel - Advanced Cell Diagnostics (ACD) Bio-Techne
Topic: Methods and technology development

Transcriptomic studies have ushered into an era of single cell technologies that are crucial for both classifying and characterizing known and novel cell populations of complex heterogenous tissues. However, such techniques are limited by the use of dissociated cells that result in the loss of spatial organization of these cell populations, thus requiring a highly multiplexed approach that can interrogate gene expression at a single cell resolution while retaining the morphological context. We sought to utilize the RNAscope HiPlex and HiPlexUp assay and reagents to spatially map diverse gene signatures identified by single cell RNA sequencing (scRNAseq) and known neuronal cell-type specific markers. With the previous HiPlex-12 reagent workflow, we spatially mapped the novel medium spiny neuronal (MSN) D1 and D2 subtypes identified by scRNAseq (Gokce et al, Cell Rep, 16(4):1126-1137, 2016). The new HiPlexUp reagent workflow enables for simultaneous detection of up to 48 targets on a single tissue section. This iterative target detection process allows for a highly sensitive and specific mRNA visualization without compromising the structural integrity of the tissue morphology. In addition to visualizing the previously confirmed major and minor D1 and D2 MSN subtypes (Drd1, Htr7, Pcdh8, Th, Synpr, Crym, Wfs1, Calb1, Drd1, Cnr1, and Foxp1) we also visualized neuronal markers (Fam84b, Lhx6, Crh, Vip, Tac1, Moxd1, Slc6a1, Sst, Chrna2, Gad2, Slc32a1, Gria1, Grin1, Cx3cr1, Chrm1, Chrm3, Oprd1, Chrnb2, Gabr2, Vglut1, Vglut2, Gad2, Calb2, and Pvalb) and ubiquitously expressed genes (Polr2a, Ppib, Ubc, Hprt, ActB, Tubb3, Bin1, Ldha, Gapdh, Pgk1, Bhlhe22, and Cplx2) of the mouse brain. The markers were expressed across various region of

interests such as the olfactory bulb, caudate putamen, Hypothalamus and Cerebral cortex. These diverse expression patterns serve as an invaluable tool is understanding the region-specific functional significance of these neuronal genes. In conclusion, single-cell transcriptomics combined with spatial mapping by the RNAscope technology is well suited for resolving heterogeneous tissues at cellular resolution and providing insights into cellular organization and function of diverse cell types in healthy and disease states.

Eventer: Software you can train to detect spontaneous synaptic responses for you

Unique Code: TP001324

Authors: Oliver Steele - Sussex Neuroscience University of Sussex, Samuel Liu - Sussex Neuroscience University of Sussex, Giles Winchester - Sussex Neuroscience University of Sussex, Wajeeha Aziz - Sussex Neuroscience University of Sussex, Andre Chagas - Sussex Neuroscience University of Sussex, Andrew Penn - Sussex Neuroscience University of Sussex,

Topic: Methods and technology development

Detection and analysis of spontaneous synaptic events is an extremely common task in many neuroscience research labs. Various algorithms and tools have been developed over the years to improve the sensitivity for detecting synaptic events. However, the final stages of most procedures for detecting synaptic events still involves manual selection of candidate events. This step in the analysis is laborious and requires care and attention to maintain consistency of event selection across the whole dataset. Manual selection can introduce bias and subjective selection criteria that cannot be shared with other labs simply in reporting methods. To address this, we have created Eventer, a standalone application for the detection of spontaneous synaptic events acquired by electrophysiology or imaging. This opensource application uses the freely available MATLAB Runtime and can be deployed on Mac, Windows and Linux systems. The principle of the Eventer application is to learn the user's 'expert' strategy for classifying a set of detected event candidates from a small subset of the data, and then automatically apply the same criterion on the whole dataset. Eventer uses a suitable model template to pull out event candidates using fast fourier transform (FFT)-based deconvolution. Random Forests are then trained to associate various features of the events with manual classification. The stored model file can be reloaded and used to analyse large datasets with greater consistency. The eventer website (https://eventerneuro.netlify.app/) includes a repository where researchers can upload and share their machine learning model files and thereby provide greater opportunities for enhancing reproducibility when analysing datasets of spontaneous synaptic activity. In summary, Eventer, and the associated repository, could allow researchers studying synaptic transmission to increase throughput of their data analysis and address the increasing concerns of reproducibility in neuroscience research.

Recording and characterising optogenetically-induced cortical spreading depression in awake mice using active graphene arrays

Unique Code: TP001328

Authors: Martin Smith - Clinical & Experimental Epilepsy University College London,

Topic: Methods and technology development

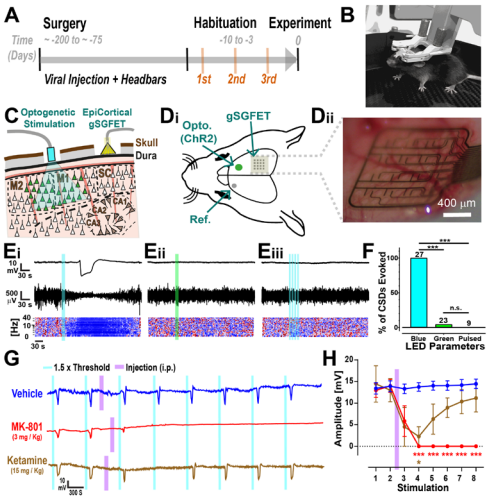
Introduction Infra-slow activity (ISA), especially cortical spreading depression (CSD) is rarely recorded in pre-clinical studies due to technical limitations. Additionally, methods to induce CSD show variability, which limits our ability to understand this energy-intense, pathological phenomena. Here, we developed a methodology utilising a type of active recording configuration, graphene solution-gated field-effect transistor (gSGFETs) arrays, in awake animals to advance

translational research into ISA, specifically CSDs .

Methods CSDs were reliably induced in head-fixed, awake mice using optogenetic methods. Using gSGFETS, propagating CSDs were electrophysiological mapped to provide spatial-temporal resolution that is superior to traditional recording methods. Finally, this assay was adapted for pharmacological screening of CSD inhibition using NMDA antagonists.

Approach for Statistical Analysis The variable of interest was isolated and modified to allow two-way repeated measures ANOVA between vehicle and compounds of interest for multiple-timepoints and standard t-tests/ one-way ANOVA between single-timepoints.

Results and Conclusions Viral vectors localised channelrhopsin expression to neurons of the motor cortex resulting in ≥1 mm3 trandsuction volume. 5-10 s of blue light induced CSDs at a propagation velocity of 3.0 ± 0.1 mm/min. gSGFETs enabled examination of CSD-induced activity suppression across frequency bands. Local differences in CSD waveform shapes were categorized into clusters. Pharmacologically, the NMDA antagonist, MK801 (3 mg/kg), suppressed CSD induction and propagation, an effect mirrored, transiently, by ketamine (15 mg/kg), thus demonstrating this models' applicability as a preclinical drug screen. The presence of CSDs, particularly if prolonged in duration and occurring at high frequency, worsens several neurological diseases and remains poorly understood, requiring more research for the development of improved therapies. Here, our anaesthesia-free in vivo assay permits minimally invasive optogenetic induction of CSD and is combined with multichannel full-bandwidth electrophysiological recordings, enabled by gSGFETs. Adoption of this technological approach could transform preclinical investigations of CSD in disease models.



Description and characterization of optogenetic-induced cortical spreading depression in awake head-fixed mice. A: Timeline of the experiment, indicating the range of time for viral expression and the habituation trials (three) to the head-fixed apparatus prior to experimentation. B: Vectorized image showing an awake mouse in the Neurotar mobile homecage head fixation system during a habituation training session. C: Sagittal schematic of the experimental arrangement, indicating ChR2 expression in frontal motor cortex areas (M1 & M2) and the epidural positioning more posterior of a 16-channel transistor array over somatosensory cortex (SC). Di-ii: (Di)Top view schematic showing the ChR2 expression areas activated by optogenetic stimulation (Opto.), gSGFET placement, and the position of the reference electrode (Ref.) in the contralateral motor cortex. (Dii) Photograph of a 4x4, 16-channel gSGFET neural array placed epidurally over the somatosensory cortex for recordings. Ei-iii: Representative data from one transistor showing DC-coupled (top; black), high-pass filtered 1-40Hz (middle; black) and z-scored power spectra of 1-40 Hz (bottom) before, during and after illumination with continuous blue light (10s) (Fi), continuous green light (10s) (Fii), or pulsed blue light (20 Hz) (Fiii). For the z-scored power spectra plots, z-score is calculated for each frequency with respect to the before (-100s to -10s) LED stimulation epoch. Colour scale goes from +2 (red) to -2 (blue) standard deviations. F: Quantification and statistical comparison of evoked CSDs success in response to continuous blue light illumination (n = 27 animals), continuous green light (n = 23 animals) and pulsed blue light (n = 9 animals). Fisher's exact test compared between groups. G: Representative DC-coupled recordings from a single transistor from an animal injected with either saline (blue), MK-801 (red) or Ketamine (Brown). The blue and magenta bars indicate the time of light stimulus and i.p. injection respectively. B: Peak amplitude of CSDs from repetitive induction of CSDs in the presence of vehicle, MK-801 and Ketamine. n (mice) = 6 Vehicle, 5 MK-801, and 3 Ketamine. Absence of CSD was considered as 0 mV amplitude. Statistics. 2-Way Repeated Measures ANOVA with Sidak's post-hoc tests to examine differences between specific stimulations

Improved spatio-temporal resolution and modular sensor development for optically-pumped magnetometer MEG

Unique Code: TP001364

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Topic: Methods and technology development

Introduction: Magnetoencephalography (MEG) is a widely used neuroimaging technique with numerous clinical applications. Technological developments with Optically Pumped Magnetometers (OPMs) have enabled new non-invasive brain function mapping capabilities with OPM-MEG, offering improved sensor placement flexibility. As sensors can be positioned closer to the scalp, compared to superconducting quantum interference devices (SQUIDs), they also offer an improved spatial resolution with increased source localisation.

In this study, we use visually evoked fields (VEF) to assess the ability of OPM-MEG to detect brain signals with simultaneously high spatio-temporal resolution.

Further improvements in spatial resolution could be achieved moving towards the use of OPM arrays, instead of single sensors. Separately, we show the first recorded brain response of our newly built modular OPM, aiming to push the transition from single sensors into calibrated OPM arrays.

Methods: We used OPM-MEG and SQUID-MEG to show a higher spatiotemporal resolution of OPM-MEG across two visual stimuli; the flash and the pattern reversal. We used two OPMs over the primary visual cortex (Oz) and the associative visual cortex (POz) to 3 healthy participants (aged 26-47 years). All MEG measurements were taken in the Ak3b MSR at PTB, Berlin.

For the new OPM testing, the sensor was placed over the Oz of two participants (aged 27-29 years). An auditory cue was used to instruct the participants to open and close their eyes every 10±1s. All measurements were taken inside a 3-layer μ-metal cylinder.

Statistical analysis: No statistical analysis as the number of participants is too small. The averaged VEF time components were analysed by measuring the Pearson correlation coefficient, signal height to width ratio, and by comparing the individual field components (radial and axial).

Results & conclusion: The evoked responses were highly reproducible with consistency across multiple participants, stimulus paradigms, and sensor modalities. A consistent time lag of 10-20 msec was observed between the Oz and POz sensors, enabling further studies of neurophysiological signal tracking. Moreover, we present clear alpha band responses recorded by our newly built OPM, paving the way for an OPM array.

Risks and concerns associated with facial Neuromuscular Electrical Stimulation (fNMES)

Unique Code: TP001374

Authors: Themis N. Efthimiou - Psychology University of Essex,Paul Hanel - Psychology University of Essex, Sebastian Korb - Psychology University of Essex,

Topic: Methods and technology development

Introduction: Facial neuromuscular electrical stimulation (fNMES) allows for the delivery of proprioceptive facial input to the CNS, which based on initial evidence can improve mood and reduce symptoms of depression. However, risks associated with NMES can be a major obstacle to its implementation in neuroscience research. In an effort to understand the communication best suited to maximise volunteers' participation and retention rate, we investigated their concerns at the prospect of participating in a hypothetical fNMES study.

Method: Likelihood of taking part (LOTP) in a study using fNMES was rated by 201 participants (100 females, mean age 27.6 years) at two time points: before and after reading detailed information about fNMES and its risks. Participants also indicated their knowledge about electrical stimulation, and their concerns about suffering burns, pain, and loss of muscle control. Moreover, questionnaires were completed measuring risk-taking, body awareness/image, and personality.

Analysis: Data were analysed using a 2x2 mixed-ANOVA with the factors Level of Information (low or high) and Gender (male, female). Finally, multiple regressions were fitted to predict LOTP based on Information. The first model was fitted with education, gender, questionnaires, and knowledge of fNMES. The second model included the same terms with the addition of their concerns.

Results: Participants' LOTP was generally high and increased based on participants' previous knowledge about fNMES, and their tendency not to worry about the sensations of pain. LOTP was inversely related to participants' concerns for burns and loss of muscle control. Interestingly, it also decreased when detailed information about fNMES' potential risks was presented ($p = .015$, $\eta p2 = .06$).

Implications: Willingness to take part in fNMES research is generally high but decreases once the associated risks are described. Increasing participants' knowledge of electrical stimulation may aid in reducing concerns and increasing retention. Further, reducing concerns specifically for burns and loss of muscle control (and less so for pain) should be beneficial. This may be accomplished by demonstrating the effects of NMES on limbs before moving to the face.

Neurodevelopment and stem cells

Investigating the Effects of 16p11.2 Deletion on Cerebral Development and Interneuron (IN) Production Using Ventral Telencephalic Organoids

Unique Code: TP001071

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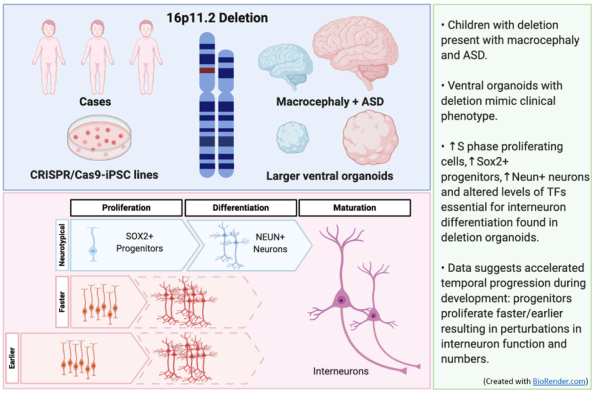
Topic: Neurodevelopment and stem cells

Introduction: Copy number variations (CNVs) of chromosomal region 16p11.2 are genetically linked to 1% of Autism Spectrum Disorder (ASD) cases. This 600kbp region contains 29 genes, but the functions of many genes in this CNV remain poorly defined. Similarly, the underlying molecular mechanisms linking the deletion to ASD pathophysiology remain largely unknown. Our work investigates whether aberrant progenitor proliferation and differentiation into interneurons(INs) are potential mechanisms that contribute to the clinical phenotypes of 16p11.2 deletion: macrocephaly and ASD. Methods: We generated ventral organoids from 16p11.2deletion-CRISPR/Cas9-iPSC lines and isogenic controls to mimic early-to-mid-foetal ventral telencephalic development. Area, maximum diameter and perimeter of organoid sections were measured across development. Organoids were fixed and examined at 35 and 65 days for immunohistochemistry and 46 and 70 days for RT-qPCR. Approach for statistical analysis: Paired t-test comparisons between deletion (del) and control organoids were made using R. Results: Del organoids were significantly larger in size ($p<0.0001$). Cell cycle analysis revealed that a higher proportion of proliferating cells were in S-phase in del organoids at 35 days. The number of Ki67+ proliferating cells declined by 65days. Gene expression analysis showed a significant increase in SOX2 (expressed in progenitors) and NEUN (expressed in neurons) mRNA expression at earlier stages in del organoids. Altered expression levels of genes encoding transcription factors essential for IN development together with perturbations in the mRNA expression of several IN subtype markers were also found. Conclusions: Larger organoid size, mimicking the macrocephalic phenotype of patients, was initially associated with increased numbers of proliferating cells. The subsequent decline in numbers of proliferating cells suggests a premature depletion of the progenitor pool and/or a shift towards asymmetric neurogenic divisions. Collectively, this suggests an accelerated temporal progression of the developmental trajectory in del organoids, whereby progenitors begin proliferation and differentiation at earlier stages, resulting in perturbations in IN function and numbers.



Protocadherin-19: Membrane to Nucleus Signalling in mESC-derived neurons

Unique Code: TP001149

Authors: Sylvia Adriana Newbold - Division of Neuroscience, School of Biosciences Cardiff University, James Wilding - Division of Neuroscience, School of Biosciences Cardiff University, Isabel Martinez-Garay - Division of Neuroscience, School of Biosciences Cardiff University ,

Topic: Neurodevelopment and stem cells

Introduction:
Mutations in the X-linked gene PCDH19 lead to epilepsy with cognitive impairment in heterozygous females. Although the gene codes for a cell adhesion protein of the cadherin superfamily expected to localize at the cell membrane, recent reports have implicated PCDH19 in the regulation of gene expression and have identified the protein in the nucleus.

Our aim is to determine if PCDH19 undergoes proteolytic cleavage resulting in the generation of an intracellular fragment (PCDH19-ICD) that translocates to the nucleus to regulate gene expression. In addition, we want to identify which genes are regulated by PCDH19 in neural progenitors and neurons.

Methods:
To test this hypothesis, we have analysed how the absence or inactivation of specific proteases affects the generation of PCDH19-ICD in heterologous cells and neurons. To determine potential transcriptional targets of PCDH19, we have generated a mouse embryonic stem cell line that overexpresses the cytoplasmic domain of PCDH19 from the Rosa26 locus (CYTO), and an isogenic PCDH19-knockout line (KO). Both lines, together with a control, have been used for RNAseq analysis.

Approach to statistical analysis:
Western blot results are being quantified and analysed using ANOVA or Kruskal Wallis tests dependent on data normality. For RNAseq, three samples from three independent differentiation experiments were used for each condition. PCA analysis and differential expression analysis were conducted on the data.

Results and conclusions:
Our results show that PCDH19 can be processed by ADAM10 and gamma secretase, and that PCDH19 undergoes activity-dependent proteolytic processing in neurons. RNAseq analysis indicates changes in several synaptic pathways in those neurons overexpressing PCDH19 cytoplasmic domain, suggesting a potential role for PCDH19 processing in the modulation of synaptic function.

We believe that PCDH19 is capable of transducing information about events happening at the membrane to the nucleus to elicit appropriate cellular responses and expect that our RNAseq analysis will provide new mechanistic insights into the function of PCDH19 both during neurogenesis and in post-mitotic neurons.

Cortical progenitors lacking Pax6 change fate when exposed to Sonic Hedgehog

Unique Code: TP001220

Authors: Maizatul Fazilah Abd Razak - Centre Discovery for Brain Sciences University of Edinburgh

Topic: Neurodevelopment and stem cells

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During forebrain development, the transcription factor Pax6 is highly expressed by progenitors in the dorsal telencephalon (dTel) i.e. the primitive cerebral cortex with a sharp boundary at the pallial-subpallial area, thereby establishing the dorso-ventral patterning of the forebrain and regulating the generation of glutamatergic neurons.

Strikingly, removal of Pax6 allows the cortical progenitors to switch fate from glutamatergic to GABAergic, indicated by ectopic gene expression. We asked what makes cortical progenitor cells change their fate when Pax6 is deleted? We postulate that Pax6 confers glutamatergic fate in progenitors by preventing them from responding to signalling cues such as Sonic Hedgehog.

In the present study, we used Pax6-floxed (Pax6fl/fl) mutant mice expressing a tamoxifen-inducible form of Cre recombinase under the control of the Emx1 locus (Emx1-CreERT2) and an EGFP reporter construct. Cultured cortical progenitors were exposed to increasing concentrations of Shh agonist, developed for the protein Smoothened, which is a key part of the activation of Hedgehog signalling pathway. Statistical analysis was done using two-way ANOVA. Significant increases of Gsx2+ and Olig2+ cells were observed in parallel with the increase of Shh agonist concentrations. We also investigated the possibility that these cells matured into interneurons (INs) after exposure to SAG, if they do have electrical properties akin to specific type of INs.

Our finding suggests that morphogens such as Shh exert a ventralizing effect on cortical progenitors, and Pax6 is required to resist such an effect in order to safeguard glutamatergic fate. These cells also have the potential to develop into a subtype of IN when exposed to SAG.

Emergence of a new FGF in the regulation of postnatal Subventricular zone (SVZ) neurogenesis

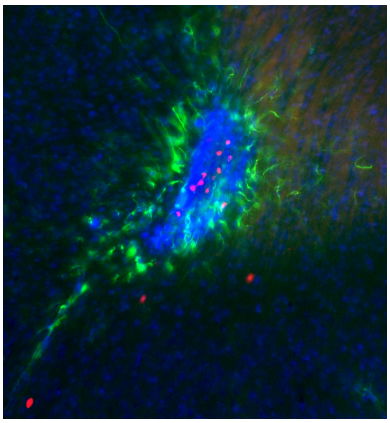
Unique Code: TP001228
Authors: Mohammad K Hajihosseini - School of Biological Sciences University of East Anglia,
Topic: Neurodevelopment and stem cells

Mohammad K. Hajihosseini, Giada Vanacore, Tianqi, Li, Andrew Hagan and David Ornitz

School of Biological Sciences, University of East Anglia, Norwich, UK; Department of Developmental Biology, Washington University School of Medicine, Saint Louis, Missouri, USA.

In the adult rodent brain, new neurons are generated daily by neural stem cells (NSC) of the subventricular zone (SVZ) bordering the lateral ventricles. Destined for the olfactory bulbs (OB), these new SVZ-derived neurons play important modulatory roles in odour-detection and the related behaviors in mice. SVZ neurogenesis is highly compartmentalized and the orderly generation of OB neurons requires the activation of NSC from their quiescent state, but the precise cohort of such activators remains unknown. Fibroblast Growth Factors (FGFs) and signaling via their receptors (FGFRs) is critical to stem cell identity, proliferation and differentiation, as well as organogenesis. Here we have analysed the expression of an FGF family member and followed the fate of FGF-expressing cells to discover an involvement in OB neurogenesis and compartmentation of the adult SVZ. We used FGF-creERT2::Rosa26-Tomatodsred double transgenic

mice (DTG) of either sex. To carry out lineage tracing, 3-month-old DTG mice were pulsed with tamoxifen for two consecutive days by oral gavage and analysed either 2 or 12 days later. In preliminary studies, n=6 for each timepoint has been analysed to detect an effect size of 0.6-0.9 with alpha level of 0.05 and power of 0.8 in two-way ANOVA tests. At each analysis time point, brains were serially section to capture the entire OB and SVZ bregma coordinates and these were subsequently immunolabelled with anti-dsred antibodies in conjunction with cell type specific markers. Anatomical distribution and abundance of dsred+ cells were noted in reference to known regional markers of SVZ and OB. In short chase experiments, dsred+ cells were largely confined to dorsal and medial aspects of SVZ, whilst in long chase experiments, dsred+ cells were additionally found in the rostral migratory stream, as well as periglomerular regions of the OBs, bilaterally. Morphology of the latter clearly resembled neurons. In a few SVZ dsred+ cells expressed GFAP. Our findings strongly indicate that there is a supply of OB neurons from the dorsal SVZ delineated by FGF expression. Moreover, as FGF-receptors are expressed by quiescent NSC in the lateral SVZ, our results now identify an FGF ligand as a potential regulator of NSC quiescence/ activation, with important implications for understanding mechanism that regulate adult neurogenesis.



Distinct embryonic progenitor pools in the ventral telencephalon generate fine-scale striatal synaptic circuits

Unique Code: TP001287

Authors: Tommas Ellender - Department of Pharmacology University of Oxford, Jack Gordon - Department of Pharmacology University of Oxford, Andrew Sharott - BNDU University of Oxford, Rohan Krajeski - Department of Pharmacology University of Oxford, Anezka Macey-Dare - Department of Pharmacology University of Oxford, Fran van Heusden - Department of Pharmacology University of Oxford,

Topic: Neurodevelopment and stem cells

Introduction:

A fundamental question in neuroscience is how neuronal identity and precise synaptic connectivity within neuronal circuits develops. Studies in dorsal telencephalon i.e. cortex have highlighted important and distinct roles for individual embryonic progenitors or distinct pools of neural progenitors, in shaping neuronal identity and synaptic connectivity in postnatal circuits. However, much less is known if and how embryonic progenitors have a similar role in ventral brain structures, such as those giving rise to the basal ganglia and striatum.

Methods:

We used in utero electroporation in prenatal C57Bl/6 mice to fluorescently label two pools of striatal embryonic

progenitors in the lateral ganglionic eminence, distinguished by their differential expression of the tubulin alpha1 (Tα1) gene, which labels Tα1-positive apical intermediate progenitors (aIP), as well as Tα1-negative other progenitors (OP) and all their progeny. In postnatal striatal tissue we used electrophysiological recordings of progenitor-derived neurons, anatomical analysis and optogenetic circuit-mapping experiments to investigate how embryonic origin of neurons shapes postnatal striatal synaptic circuits.
Approach for statistical analysis: Main datasets include measurements of intrinsic electrical and morphological properties, connectivity incidence and synaptic strength. All data is tested for normality and statistically compared using appropriate parametric (e.g. Student's t-tests), non-parametric (e.g Wilcoxon signed-rank) or other tests (e.g. Fisher's exact).

Results and conclusions:
aIP and OP embryonic progenitors generate direct and indirect pathway spiny projection neurons (SPNs) with similar electrophysiological and anatomical properties found intermingled in medial striatum. Optogenetic circuit-mapping experiments demonstrate that progenitor origin impacts long-range excitatory input strength, with medial prefrontal cortex preferentially driving aIP-derived SPNs and visual cortex OP-derived SPNs. In contrast, the strength of local inhibitory inputs amongst SPNs was controlled by birthdate rather than progenitor origin. Combined, these results demonstrate distinct roles for embryonic progenitor origin in shaping the neuronal and circuit properties of the postnatal striatum.

The role of Lis1 in the inhibitory circuits in a mouse model for neurological disorders

Unique Code: TP001313
Authors: Ana Maria Jimenez - Experimental embryology Instituto de Neurociencias (UMH-CSIC),
Topic: Neurodevelopment and stem cells

Type I lissencephaly is a severe developmental brain disorder in humans caused by mutations in Lis1 gene. Lis1 mediates neuronal migration in developing brain, regulates dynein-dependent axonal transport and supports synaptic integrity in mature brain. Though Lis1 is expressed throughout the entire lifespan, little is known about its potential role in the maturation of the nervous system.

The physiological development of the cerebral, hippocampal and cerebellar cortices, and the formation of neuronal circuits involve precise cortical neuronal differentiation and migration. Disruption of the balanced and coordinated excitatory pyramidal neurons and inhibitory interneurons can result in neurological disorders including: epilepsy, schizophrenia, as well as autism. Parvalbumin (PV) is highly expressed in cortical interneurons in adult mouse and its expression is delayed until birth. Similarly, immature cerebellar cells originated from the external and internal granular layer migrate after birth. For these reasons we examine the effects of inactivating Lis1 expression in PV cells in prepubertal mice.

Neuronal migration and integrity of neural circuits have been characterized with the conditional Lis1 knockout mice in PV+ (Lis1cKO-PV+) after birth, using extracellular recordings and immunolabelling assays (immunofluorescence, iDISCO & In Situ Hybridization) to detect cortical and cerebellar neurons. Visualisation and neuronal cell quantification using Confocal microscope, Thunder microscope, Imaris and ImageJ.

Descriptive statistical analysis and graphical analysis will be carried out with RStudio 3.6.1 and it will be presented as

"mean (SD)". The data from immunofluorescence studies will be express as "age or genotype increased mean of number of neurons by x ± SEM (n=z; P < 0.05)". Assuming the data follows normality and quality of variance, parametric methods will be used such as analysis of variance and paired t-test followed by Tukey HSD post hoc test. Linear or Multiple regression will be performed if it is required. A value of P<0.05 will be considered to be significant.

The deletion of Lis1 expression in PV cells produce a severe phenotype observed in Lis1cKO-PV+ postnatal mice, characterised with a hippocampal heterotopy and abnormal morphology of PV interneurons. It also causes a histological difference in PV expression in CA2 and CA3 in the hippocampus, a selective decline in PV+ dendritic tree and disorganisation of Purkinje cells. Surprisingly, the conditional mutant mice present enlarged ventricles and an ataxia, which can be representative of the dysfunctional cerebellum.

The loss of Lis1 in parvalbumin cells alters the neuronal migration and integrity in the mature murine nervous system. Electrophysiology studies will determine the functionality of Lis1 in the neural connectivity in cortical pathways, ad hippocampal and cerebellar neuronal projections in the mutant mice.

Neurons and glia: intrinsic properties, cell biology and cell types

The Role of Microglia in CNS Innate Immune Memory

Unique Code: TP001045
Authors: Reiss Pal - The Roslin Institute and R(D)SVS The University of Edinburgh, Barry Bradford - The Roslin Institute and R(D)SVS The University of Edinburgh, Abigail Diack - The Roslin Institute and R(D)SVS The University of Edinburgh, Neil Mabbott - The Roslin Institute and R(D)SVS The University of Edinburgh,
Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Microglia are heterogenous mononuclear phagocytic immune cells of the central nervous system (CNS) and their functions aim to maintain brain homeostasis. CNS immune plasticity permits either immune training or tolerance against previously challenged pathogenic stimuli, which serves to exacerbate or repress the neuroinflammatory response, respectively. Here, it is hypothesised that microglia are required for executing CNS immune memory. To test this, the Csf1rΔFIRE/ΔFIRE transgenic mouse model was assessed for the presence of CNS immune memory. This model contains a deletion of an intronic enhancer sequence of the colony stimulating factor 1 receptor (Csf1r) gene and are absent of microglia from birth.

C57BL/6J and Csf1rΔFIRE/ΔFIRE mice received an intraperitoneal injection of liposaccharide (LPS) as a single challenge (1x) or once every 24 hours over 4 consecutive days (4x). 3 hours post final injection mice were sacrificed. Brains were assessed by reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) for transcriptional profiling. Hippocampal and microglial images were collected after immunohistochemistry.

Mice were grouped according to their respective treatment and confirmed genotype. Image and gene expression analyses were performed using One Way ANOVA/ Post-Hoc Tukey test. Significance was defined by p<0.05.

In C57BL6/J mice, a single challenge of LPS induced CNS neuroinflammation through transcriptionally up-regulating pro-inflammatory factors. However, the transcriptional induction of these pro-inflammatory factors was significantly weaker after 4x LPS treatment. This is indicative of CNS immune tolerance following subsequent LPS challenges, and thereby

supports the presence of immune memory. Transcriptional upregulation of microglial associated markers was likewise detected after 4x LPS treatment. Moreover, the Csf1rΔFIRE/ΔFIRE model was identically treated and the transcriptional responses of these inflammatory and microglial markers will be measured. This will identify whether CNS immune tolerance to systemic LPS is consistent in the absence of microglia. Taken together, the Csf1rΔFIRE/ΔFIRE model will provide further insight into the participation of microglia in the process of CNS immune tolerance.

Characterisation of Glial & Neuronal Pathology Associated with A? Proteins in an Alzheimer's Disease Model

Unique Code: TP001082

Authors: Jiabin Tang - Brain Sciences Imperial College London, Steve Gentleman - Brain Sciences Imperial College London, Paul Matthews - Brain Sciences Imperial College London,

Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Introduction: Alzheimer's Disease is the most common type of late-life dementia, and there are several pathological hallmarks, including Aβ deposition, neurofibrillary tangles, glial activation, neuronal death and synaptic loss. However, although Aβ deposits are surrounded by activated microglia and astrocytes in AD, it remains uncertain whether this is a consequence of the Aβ plaques or whether they contribute to their genesis. The relation of these two pathological elements to neurodegeneration also remains surprisingly unclear. In this study, we focused on early stage AD pathology, using the App<NL-G-F> mouse model. This is a novel triple knock-in model in which there is early-stage Aβ42 protein pathology without overexpression of other APP components.

Methods: We have 6 App<NL-G-F> and 6 wildtype mice at three different ages (2.5, 7, 12 months). Sections were stained from both frontal cortex and hippocampus. We have characterized 12 markers related to the pathological hallmarks using immunohistochemistry. These include Aβ plaques, Aβ oligomers, synapses, as well as different functional phenotypes of microglia and astrocytes.

Approach for statistical analysis: Two-way ANOVA has been carried out when comparing genotypes, genders and age groups.

Results and conclusions: We have observed no change of overall microglia density, but the astrocyte density and microglia phenotypes have changed significantly, coincident with Aβ pathology. We have shown that the Aβ oligomer expression level kept increasing across the three timepoints, even when Aβ deposition plateaued after 7 months. Previous literature suggests that obvious cognitive deficits only appear after 12 months, indicating that Aβ oligomers, rather than Aβ deposits, that cause these deficits. We have demonstrated that microglia phenotypic changes, to a more activated state, are coincident with the extent of Aβ plaques. In addition, Aβ oligomer expression levels tend to correlate more closely with astrocyte activation rather than microglia phenotype change. We believe that further characterization of this model will give us insights into the early stages of AD pathology.

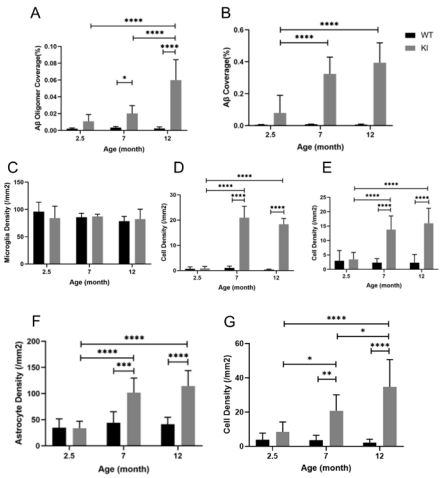


Figure 1. IHC analyses characterizing of different pathological markers in hippocampus and frontal cortex. (A) Aβ oligomer coverage. (B) Aβ deposition coverage. (C) Overall microglia (IBA1+) density. (D) Activated microglia (CD68+) density. (E) Proinflammatory microglia (CD16/32+) density. (F) Overall astrocyte (GFAP+) density. (G) Proinflammatory microglia and astrocyte (PBR+) density.

Investigating the influence of astrocytes on microglia phenotypes in an induced pluripotent stem cell model of Huntington's Disease

Unique Code : TP001083

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Huntington's disease (HD) is a severe neurodegenerative disorder caused by a dominantly inherited CAG trinucleotide repeat expansion in the huntingtin gene (HTT). Even though neuroinflammation is a prominent sign in many neurodegenerative disorders, its contribution to HD pathology is not well understood. Activated microglia and reactive astrocytes might contribute through transcriptional activation of pro-inflammatory genes to sustain a chronic inflammatory state. However, the influence of mutant HTT expression on microglia morphology and function, as well as the effect of HD astrocytes on microglia phenotypes are still unknown. We used patient-derived induced pluripotent stem cell (iPSC) models of HD microglia and astrocytes with 109 CAG repeats and isogenic controls with a corrected wild-type CAG length of 22 repeats. In order to investigate if astrocytes affect microglia via secreted factors or by physical contact, we used astrocyte-conditioned medium (ACM) on microglia monocultures as well as established an astrocyte-microglia coculture system. We found that HD microglia exhibit a less ramified phenotype, with significantly decreased cell area and complexity, compared to isogenic controls. The phagocytosis of pathogens, apoptotic cells and debris is a key feature of microglia function. Phagocytosis of E. coli beads was significantly decreased in HD microglia compared to controls. Differentiation with the addition of HD ACM did not have an effect on HD or control microglia morphology and phagocytosis. However, in co-culture with HD astrocytes, both HD and control microglia phagocytosed significantly more E. coli beads compared to the co-culture with control astrocytes. Our data suggest a cell-autonomous effect of mutant

HTT expression on microglia status and activity and report that physical contact with astrocytes can affect microglia function, thus supporting the use of iPSC-derived monoculture and coculture models to study neuroinflammation in HD.

DIFFERENT CELLULAR SUSCEPTIBILITY TO MITOCHONDRIAL DYSFUNCTION AFTER NEONATAL AND CHEMICAL HYPOXIA BETWEEN ASTROCYTES AND NEURONS

Unique Code: TP001086
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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

The relationship between hypoxia and psychiatric illnesses is known mainly due to the association of placental vasoconstriction and changes in neurodevelopment. Because hypoxia modifies energy production and, therefore, mitochondrial metabolism and dynamics, our goal was to evaluate mitochondrial function in primary culture of astrocytes and neurons after chemical and neonatal hypoxia; Cobalt Chloride (CoCl2 - 800 µM and 2 mM for 24 hours) induced chemical hypoxia, and neonatal hypoxia is observed in the Spontaneously Hypertensive Rats (SHR) animal strain. Cells were then loaded with i) Fluo-4-AM (10 µM) to measure calcium levels, ii) TMRE (500 nM) to analyze mitochondrial membrane potential, and iii) H2DCF-DA (20 µM) and Mitosox (5 µM) to investigate redox homeostasis. Moreover, real-time PCR were performed to verify the expression of genes related to mitochondrial metabolism and biogenesis, also high-energy compounds was investigated. Astrocytes and neurons after chemical or neonatal hypoxia presented disturbances in Ca2+ handling, depolarized mitochondria, and alterations in redox system with an increase in reactive oxygen species (ROS) and superoxide levels concomitant with a disturbance in Nfe2l2 expression. In addition, hypoxia promoted alterations in ATP, Pyruvate and Lactate levels, concomitant to modification in NAD+/NADH ratio in both cells' types. Interestingly, the SHR cells showed increased expression of genes related to mitochondrial content, as Pgc1a, Nrf1, Tfam, MtCo1 and Tom-20 in astrocytes, but not in neurons. The two-way Anova followed by post-hoc of Bonferroni were used as statistical analysis. A probability of $p<0.05$ was considered significant in all comparisons. Altogether, our data suggest that hypoxia can induce mitochondrial deregulation and decrease energy metabolism in the most prevalent cell type in the brain, astrocytes. Contrarily, neurons also presented mitochondrial disturbances and alterations, but responds differently to hypoxia revelling milder modifications with higher increase in pyruvate co-occurring with lower generation of lactate. These data contribute to an enrichment in hypoxia effects on brain regarding each cell type and highlight an important venue of research field on neurodevelopmental disorders.

A role for brain-derived neurotrophic factor in new myelin formation during long-term spatial memory consolidation

Unique Code: TP001110
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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Myelin is a sheath of multi-layered specialised membrane formed around axons, which increases the speed of action potential propagation during synaptic transmission. Myelin in the central nervous system (CNS) is produced by oligodendrocytes (OLs) and the adult rodent brain retains the ability to produce new myelinating OLs through the differentiation of oligodendrocyte precursor cells (OPCs). There is growing evidence that brain derived neurotrophic factor (BDNF) may have a pro-myelinating effect in the CNS, however, the mechanisms of this process remain unclear. Gaining further insight is therefore critical for the potential development of therapeutics to treat conditions such as

stroke and traumatic brain injury where significant damage to CNS myelin is sustained and impaired spatial memory can manifest. Here we investigated the effect of BDNF tropomyosin-related kinase (Trk) B receptor agonist 7,8-dihydroxyflavone hydrate (DHF) administration on spatial learning and memory via newly formed OLs. Mice with a conditional knock-out of OPC myelin regulatory factor (MyRF-/-) were tested in the Morris water-maze (MWM). MyRF-/- mice and their hemizygous siblings (MyRF-/+) underwent seven days of MWM training. Immediately following each training session they were systemically administered DHF or vehicle. The long-term memory (LTM) retention of the mice was assessed 28-days later. We found using analysis of variance that spatial memory acquisition was unimpaired in MyRF-/- mice compared with MyRF-/+, whereas LTM was impaired in keeping with previous research. Initial findings indicate that systemic administration of DHF immediately following training rescues the memory impairment observed in MyRF-/- mice. In conclusion, this suggests that newly formed oligodendrocytes are required for long-term spatial memory consolidation and that this effect is facilitated by BDNF signaling via TrkB receptors.

Axon-targeting motifs increase trafficking of ?9 integrin in differentiated PC12 cells

Unique Code: TP001124

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

The poor regeneration of axons in the central nervous system represents a major barrier for recovery of sensorimotor function following spinal cord injury. After spinal cord injury, activated astrocytes secrete extracellular matrix proteins that inhibit axon regeneration such as tenascin-c. Our previous results have shown that viral-mediated expression of α9 integrin can enhance regeneration of adult dorsal root ganglia axons on tenascin-c substrates in vitro and into tenascin-c rich spinal cord lesion sites in vivo. In mature cortical neurons however, exogenously expressed α9 integrin is excluded from the axon potentially limiting its growth promoting effect.

Therefore, we hypothesise that expression of α9 integrin tagged with an axon-targeting motif could enhance its trafficking to the growth cone resulting in enhanced axon regeneration on tenascin-c. Using a neuron-like model of intracellular α9 integrin trafficking, differentiated PC12 cells were transiently transfected with axon-targeting motif-tagged α9-GFP constructs. Using immunocytochemical staining for GFP, the ratio of fluorescence intensity between the distal and proximal 30 µm of each neurite over 100 µm in length was measured in at least 30 cells per group. The ratios of distal:proximal fluorescence intensity of the axon-targeting motif-tagged α9-GFP groups were compared to those of the non-targeted α9-GFP group using one-way ANOVA with Dunnett's multiple comparisons post-hoc test.

Our findings indicate there was a significant effect of addition of axon-targeting motifs to α9-GFP on the distal:proximal ratio of fluorescence intensity [$F(12, 396) = 2.338$, $p = 0067$] in certain groups. Dunnett's multiple comparisons test revealed that axon-targeting motifs derived from GAP-43 (short, $p = 0.0097$; long, $p = 0.0005$), Nav1.2 ($p = 0.0478$) and neurexin ($p = 0.0121$) increased the mean distal:proximal ratio of fluorescence intensity compared to non-targeted α9-GFP ($M = 1.273$). These results show that α9 integrin can be targeted to the distal neurite of neuron-like differentiated PC12 cells. Further experiments will be required to investigate whether this is also possible in primary cortical neurons that exclude exogenously expressed α9 integrin from the axonal compartment upon maturation.

Myelination induces axonal hotspots of vesicle fusion that accelerate sheath growth in vivo

Unique Code: TP001160

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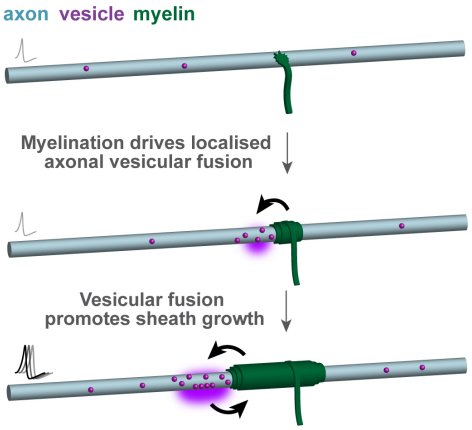
Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Introduction: Myelination drastically changes the conduction properties of axons and provides them with metabolic support. Dynamic changes to myelination occur throughout life, and those changes induced by neuronal activity are increasingly implicated in nervous system formation and function. However, the cellular bases of activity-dependent regulation of myelin, in vivo, are unclear. For example, activity might regulate myelin through the fusion of synaptic vesicles containing neurotransmitters, but it is unclear whether synaptic vesicle fusion occurs non-synaptically along the axon, directly onto myelin sheaths. Furthermore, it is unclear whether vesicle fusion precedes and biases initial myelin formation or consolidates myelination later on.

Methods: To study how axons convey activity information to their myelin sheaths, we imaged synaptic vesicle fusion along intact, individual axons in the living zebrafish spinal cord using genetically-encoded reporter SypHy.

Approach for statistical analysis: Statistical differences in vesicle fusion between distinct neuron regions, between wildtype and hypomyelinated myrf mutants, and between control and chemogenetically-stimulated animals were tested using parametric (t-test) and non-parametric (Mann-Whitney) tests, with statistical significance set at $p < 0.05$.

Results and Conclusions: We found, surprisingly, that vesicle fusion along reticulospinal axons is as frequent as at presynaptic terminals in collateral branches. Remarkably, axonal vesicle fusion was reduced in hypomyelinated myrf mutants, indicating that myelination normally drives axonal vesicle fusion. Within myelinated axons, vesicle fusion became enriched along the non-myelinated regions, concentrating near the lateral edges of myelin sheaths. This suggests direct regulation of sheath growth at these sites by vesicle cargo. Furthermore, stimulating neuronal activity promoted axonal vesicle fusion and accelerated sheath growth. Our results identify a novel 'feedforward' mechanism whereby myelination drives the neuronal activity-regulated signal, axonal vesicle fusion, that in turn consolidates myelin sheath growth.



The impact of T cells in Parkinson's Disease

Unique Code: TP001169

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Parkinson's disease (PD) is the most common neurodegenerative movement disorder. Motor and non-motor impairments are caused by the loss of dopaminergic neurons (DaNs) in the substantia nigra pars compacta (SNpc) of the midbrain. Among the main causes of PD is the aggregation of alpha-synuclein (α-syn), which in pathologic conditions can assemble in several conformational species. Recent studies showed that the exposure of peripheral blood cells (PBMCs) to α-syn-derived peptides triggers T cell responses in PD patients, thus highlighting an important role of the adaptive immune system in the disease. Candidate gene and GWAS studies revealed the association of class I and II Human Leukocyte Antigens (HLAs) alleles to PD, indicating that individuals carrying particular HLA types may be prone to develop the disease. This study aims to elucidate the role of T cells in the immune response against α-syn species administered in different conformational states and seeks to identify T cell subsets that are pivotal in the process. Additionally, we intend to characterise the response of T cells to autologous iPSC-derived DaNs in a preliminary co-culture model.

PBMCs from sporadic PD patients and healthy controls were insulted with three α-syn species and tested for their response via dual ELISpot (IFNy, IL13) and FACS analysis. On day 14 cells were harvested to perform qPCR on immune checkpoint inhibitors. iPSC-derived DaNs were generated to perform autologous T cells-DaNs co-culture experiments. Statistical analysis was performed using GraphPad. Data were normalised to the untreated control and parameters for the exclusion of data have been designed.

PBMCs from patients and controls treated with α-syn species showed variable responses via ELISpot and FACS analysis, although monomeric α-syn had a higher impact on the PD group. A difference in the expression of immune checkpoint inhibitors (CTLA4, PD1) between patients and controls was detected by qPCR. Co-culture of autologous T cells and iPSC-derived DaNs will be performed to measure differences in neuronal death between patients and controls. Our study shows that monomers can trigger responses in the PD group, and that patients and controls react differently to the α-syn insult.

Evaluation of astrocyte morphology in a mouse brain

Unique Code: TP001173

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Non-neuronal glial cells are essential components of a healthy brain. Astrocytes, a type of glial cells, maintain a plethora of functions including neuronal processing, synaptic plasticity, and ion homeostasis. Astrocyte functions directly relate to their morphology since astrocytes tightly enwrap synapses to control signal transmission in the brain. This study focuses on investigating astrocyte morphology in a ventromedial nucleus of hypothalamus (VMH) and a dorsal raphe nucleus (DRN) – brain areas integrating responses to stressful stimuli and metabolism regulation.

To quantify astrocyte morphology we employed GFAP immunohistochemistry on coronal brain sections of adult C57Bl/6 female mice combined with a detailed post-hoc image analysis in ImageJ.

We observed that total length and number of processes of DRN astrocytes are significantly decreased compared to VMH astrocytes (length: VMH astrocytes = 319±3.7µm vs DRN astrocytes = 205±2.6µm, $p<0.001$ unpaired t-test; number: VMH astrocytes = 33±0.4 vs DRN astrocytes = 19.7±0.2, $p<0.001$ unpaired t-test). When we examined this difference in detail, we observed that number and length of primary processes are similar between DRN and VMH astrocytes. However, number and length of secondary and tertiary processes is significantly reduced in DRN astrocytes in comparison to VMH astrocytes. Subsequently, DRN astrocytes were found to have lower ramification index (VMH astrocytes = 7.6±0.1 vs DRN astrocytes = 5.33±0.1, $p<0.05$ unpaired t-test) and smaller area they occupy (VMH astrocytes = 2401.1±29.0µm2 vs DRN astrocytes = 1489.9±14.5 µm2 $p<0.001$ unpaired t-test) in comparison to VMH astrocytes.

Thus, altogether these data suggest that DRN astrocytes are smaller and their morphology is less complex compared to VMH astrocytes (Figure). Such phenotype of GFAP-positive DRN astrocytes is likely to reflect decreased number and total area occupied by their finer processes compared to VMH astrocytes – however, a different technique would be required to investigate it in detail.

This study is the first step towards understanding the significance of molecular milieu within VMH and DRN that define astrocyte morphology and subsequently their functions.

Analysis of neural cells and lipid droplets in Transport Protein Particle complex subunit 9 (Trappc9) Knock-Out Mice

Unique Code: TP001174

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Introduction: Transport Protein Particle complex subunit 9 (Trappc9) is a subunit of the TRAPPII complex, which is crucial for intracellular trafficking processes as a tethering factor. Trappc9 also works as a GEF to activate Rab18, a protein that regulates lipid droplet (LD) formation and trafficking. Lipids are essential for neuronal differentiation and synaptic plasticity. Lipid metabolism abnormalities have been linked to various neurological disorders. Homozygous TRAPPC9 mutations in humans lead to microcephaly, intellectual disability and obesity. Abnormalities of white matter tracts in the cerebellum and corpus callosum have also been reported. Currently, the mechanism of Trappc9 involvement in these phenotypes has not been elucidated.

Methods: This study aims to understand the cellular function of Trappc9 and its role in brain development and body weight regulation using a novel Trappc9 knock out (KO) mouse model. Brain and body weight were analysed. Brain sections and primary cells were analysed using immunohistochemistry, immunocytochemistry and molecular techniques. Statistical analysis was performed using t-test.

Results: Trappc9 expression was observed in many neurons, e.g. in the cerebral cortex, hippocampus and hypothalamus (Arcuate and Paraventricular nuclei). Homozygous knock-out brain weights are ~10% reduced in adult mice. Body weights of KO mice were observed over nine months on chow diet and showed a gradual increase to ~22% above WT levels. This observation was more significant in females than in males. Neural progenitor cell proliferation and viability was analysed in neurosphere cultures from neonatal mice but showed no significant difference between WT and KO. In neural cell cultures from KO mice, abnormalities in lipid droplet number and size were observed as there were a decrease of total number and increase of LD size in KO cells.

Conclusion: Our data confirm that Trappc9 deficiency in mice leads to postnatal-onset microcephaly and increased adiposity, which recapitulates the human disease symptoms. These findings could be related to lipid droplet dysfunction. Further analysis is warranted to understand the role of Trappc9 in lipid droplet regulation in neural cells.

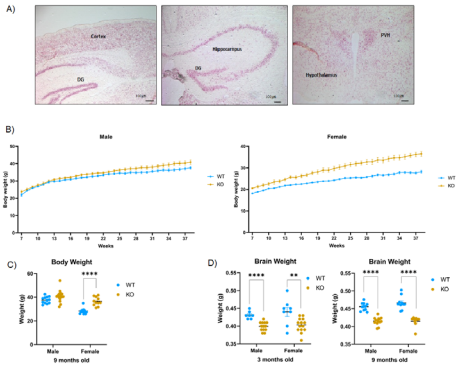

Figure: Analysis of brain and body weight in Trappc9 KO mice. A) In situ hybridisation (RNAscope) of Trappc9 in different brain areas of wild type (WT) mice. The results show wide expression of Trappc9 in the cerebral cortex, hippocampus and hypothalamus (pink signal). DG: dentate gyrus, PVH: paraventricular nucleus. Scale bars: 100 µm. B) Graph line represents male and female body weights. The weight change was more significant in females than in males. C) Body Weight change by 9 months. KO mice gained more weight than WT. D) Weight of PFA fixed brains at the age of 3 and 9 months. There is a reduction in brain weight in KO mice. Error bar: SEM. Stars: p.value, **>0.01 and ****>0.0001.

Characterisation of a unique sub-population of microglia in the embryonic forebrain

Unique Code: TP001208

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Introduction: Multiple sub-populations of microglia with distinct transcriptional profiles have recently been identified in early brain development. Little is known about how these distinct transcription patterns affect the cell biology of these sub-populations or how they are involved in forebrain development. Here we identify an undefined embryonic forebrain microglia population.

Methods: Developmental microglia associated markers were immunolabelled and visualised using confocal and fluorescence microscopy to identify forebrain microglia populations. In situ hybridisation was used to label developmental macrophage transcriptional markers and distinguish between different microglial populations.

We performed birthdating experiments by injecting Bromodeoxyuridine (BrdU) into pregnant dams to identify when microglia were born.

Finally, semi-automated morphological analysis of brain macrophages was performed to define microglia sub-population morphology.

Approach for statistical analysis: One-way ANOVAs were performed to uncover differences in expression of developmental microglia markers between embryonic timepoints. This method was also used to identify differences in birthdating between microglia populations, when injected with BrdU. Similarly, one-way ANOVAs were performed to detect differences in morphological features between microglial populations.

Results: Immunolabelling and in situ hybridisation revealed a small population of microglia near the corpus callosum which express a unique set of molecular markers, not previously described in forebrain microglia during development.

Our birthdating experiments indicate that the developmental dynamics of these microglia strongly diverges from cortical microglia.

Morphological analysis provided a basis from which to investigate functional properties of these microglia.

Conclusions: We identified a unique microglia population with an expression profile not yet observed at this stage of development. Birth dating confirmed that this is a distinctive microglial population. The precise location of this macrophage population suggests a role in corpus callosum development, a hypothesis currently under investigation.

OPA1 isoform expression and GTPase activity is significantly altered following neonatal hypoxic-ischaemic brain injury

Unique Code: TP001233

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

1. Introduction

Hypoxic-ischaemic encephalopathy affects 2-3 in every 1000 term infants and can bring about life-changing neurological consequences or death. Perturbation of mitochondrial function and subsequent induction of cell death pathways are key hallmarks in neonatal hypoxic-ischaemic (HI) injury, both in animal models and in term infants.

OPA1 is a dynamin-related guanosine triphosphatase, regulating both mitochondrial cristae junction formation and mitochondrial dynamics. Physiological function of OPA1 is mediated by interaction of its short (S-OPA1) and long (L-OPA1) forms generated by balanced action of Yme1L and Oma1 proteases. Previously we found that OPA1 was pathologically processed in in vitro and in vivo models of HI.

2. Methods

The Rice-Vannucci model of unilateral carotid artery ligation was used to induce hypoxia-ischemia in vivo in term-

equivalent, postnatal day 9 pups. Brains were collected between 0-72h post injury. Sham and untreated animals were included at all time points. OPA1 isoform expression was analysed western blot. OPA1 activity was determined ex vivo by GTPase assays of isolated OPA1 immune complexes.

3. Approach for statistical analysis
Experiments included a minimum of three males and three females per condition/time point. Statistical analysis was performed using GraphPad Prism 9 Software. Data were assessed by a Student's t-test, One-way ANOVA or Two-way ANOVA with appropriate post hoc tests as necessary.

4. Results and conclusions
Following HI, L-OPA1 is excessively cleaved to S-OPA1 which is most evident at 24h post injury, leading to an imbalance of isoform expression. Interestingly a novel, very short OPA1 cleavage product is repeatably observed HI samples, peaking at 24h post injury. Although OPA1 isoform expression is partially restored as injury evolves, we found a significant reduction in OPA1 GTPase activity at 48h post injury.

OPA1 warrants further investigation to determine its role in the regulation and recovery of mitochondrial dynamics following HI injury. Pharmacological interventions aimed at restoring OPA1 activity may provide additional methods of neuroprotection, where current therapies alone are inadequate.

The role of glial cells in Alexander's Disease

Unique Code: TP001239
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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Background
Alexander's Disease (AxD) is rare neurodegenerative disorder caused by mutations in the gene encoding a major intermediate filament protein in astrocytes, GFAP. It is characterized by white matter degeneration related to the loss or lack of myelin, as well as abnormal protein aggregates in astrocytes, known as Rosenthal Fibres. In animal models of AxD, upregulation of proinflammatory chemokines and microgliosis have been shown, particularly surrounding astrocytes. In humans, microglia have also been shown to acquire a more reactive morphology with thickened processes and enlarged cell bodies and there is also evidence of microglia phagocytosing astrocytes. However the phenotype of microglia in human AxD brains has not been extensively characterised.

Methods
To characterise the neuroinflammatory environment in AxD, we acquired FFPE brain tissue from 4 AxD patients and 6 gender and age matched controls, via BRAIN UK. Using immunohistochemistry, tissue was stained with 5 microglial markers (Iba1, HLA-DR, CD68, CD16 and CD64) and 3 astrocytic markers (GFAP, Glutamine Synthetase and EAAT2). We assessed the protein load of these markers in regions of white and grey matter that showed evidence of pathology, displaying Rosenthal fibres. Data were analysed for significance using a Mann Whitney test.

Results
CD16 protein load was significantly increased in the grey (p=0.0087) and the white (p=0.001) matter in AxD; while the other microglial markers were not affected. GFAP was significantly increased in the grey matter (p=0.0021) and Glutamine Synthetase in the white (p=0.0007) matter. EAAT2 shows no difference between the groups.

Conclusion
Our findings imply a role for antibody-dependent cellular toxicity and impaired glutamate synthesis in AxD potentially as the result of a dysregulation in the microglia-astrocyte communication.

Biochemical transformation of SH-SY5Y cells upon differentiation

Unique Code: TP001245
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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Introduction:
Neuronal models are widely used in research. SH-SY5Y human neuroblastoma cells can serve as neuron-like cells when differentiated properly. Some studies use SH-SY5Y cells as neuronal models in undifferentiated form. Previously, we have shown the potassium currents are dominant in undifferentiated cells. Sodium currents appear higher with differentiation ($P<0.05$). Also, the undifferentiated cells have three times lower Young's moduli than differentiated cells ($P<0.01$)1. Here, we investigated the changes in the expression of beta-III tubulin, synaptophysin, F-actin, and compared neurite length upon differentiation with RA+BDNF.

Methods:
SH-SY5Y cells were differentiated as explained1. Experimental groups were; undifferentiated (UNDIFF), 1 M retinoic acid + 10 ng/mL BDNF differentiated (RB).

Western blot was used to compare protein expressions. F-actin and DAPI fluorescence was used to visualize cytoskeletal structures, count the number of cells, and measure neurite length.

Approach for statistical analysis:
ANOVA and Tukey tests were performed. $P<0.05$ was considered significant, n represents the number of samples.

Results and conclusions:
F-actin and DAPI staining (n=5; Fig. 1) showed F-actin expression per nuclei was the same. Filaments were gathered closer to the nuclei in the UNDIFF cells. In the RB group, the F-actin bands were structurally organized, elongated through neurites.

Number of cells was higher in the UNDIFF group ($P<0.05$). After normalization against the number of DAPI stained nuclei, neurite length was shorter in UNDIFF cells ($P<0.001$).

According to the Western blot analysis, RB group had increased beta-III tubulin (n=5; P<0.05). Synaptophysin expression was lower in RB group (n=4; P<0.05).

According to our results, significant increase of beta-III tubulin with differentiation shows the neuron-like structure of differentiated SH-SY5Y cells. Besides, it is known that expression of potassium channels is higher in some cancerous cells compared to normal counterparts2. Combined with our previous results and the literature, these data indicate the possibility of targeting malignant cells via potassium channels.

1. Şahin M, et al. (2021) Neurosci Lett.
2. Pardo L, et al. (2013) Nat. Rev. Cancer

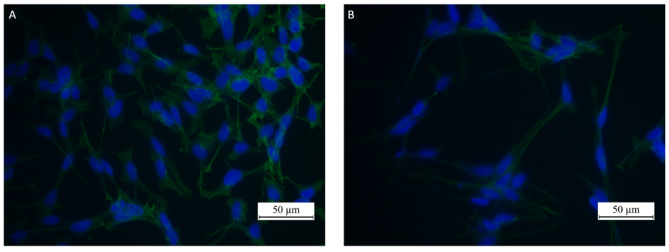

Figure 1: Superimposed F-actin (green) & DAPI (blue) staining images showing the number of cells, and structural organization of F-actin filaments. A) UNDIFF, B) RB.

Visual Cortex Neurons Driving Neurovascular Coupling During Visual Stimulation

Unique Code: TP001252

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Introduction

Neurovascular coupling is the mechanism whereby blood vessels dilate to supply energy in the form of oxygen and glucose to active neurons. Blood oxygen level-dependent (BOLD) fMRI is commonly used to measure changes in blood flow and infer neuronal activity. Yet, interpretation of the BOLD signal is limited by a lack of understanding regarding how the activity of various neuronal subtypes and BOLD are related.

Methods

Thy1-GCaMP6f and SST-GCaMP6f mice with a cranial window over V1 were imaged using two-photon microscopy to visualise excitatory pyramidal cell and somatostatin interneuron (SST) activity respectively. Mice were head-fixed while awake and allowed to locomote on a cylindrical treadmill. Thick (0.04 cycles per degree) and thin (0.2 cpd) striped drifting gratings were presented on monitors at a 45 degree from vertical angle, at 100%, 60%, 25% and 5% contrast, with the aim of differentially altering levels of activity across neuronal subtypes.

Approach for statistical analysis

We used a linear regression to examine the relationship between calcium and vessel diameter responses split by neuronal subtype, contrast and stripe condition. We compared neuronal subtypes across measures of neurovascular coupling (e.g. stimulation-dependent calcium peak sizes, local calcium activity dependent vessel dilation responses) using a linear mixed model approach.

Results and conclusions
Grating contrast most strongly modulated vessel and pyramidal cell responses. However, when vessel and calcium responses were plotted against each other, only SST calcium changes correlated with the size of vessel responses, suggesting neurovascular coupling more strongly reflects SST than pyramidal cell activity.

Investigating the role of intron retention in FUS protein autoregulation and its relevence to ALS/FTD

Unique Code: TP001258

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

1.Introduction
Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are clinically linked neurodegenerative disorders that can both be caused by mutations in the RNA-binding protein FUS. Disease causing mutations in FUS cause mislocalisation of the protein into the cytoplasm and there is evidence that FUS autoregulation is affected, but the mechanism of FUS autoregulation is not clear. We hypothesize that the FUS protein autoregulates its own expression by binding within the introns of the FUS transcript, promoting the production of an intron-retained isoform of FUS mRNA when nuclear FUS levels are high. Recently, we observed retention of introns 6 and 7 in FUS mRNA in mouse and human neuronal cells, and that cytoplasmic mislocalisation of FUS protein leads to a decrease in the expression of this FUS intron-retained transcript (FUS-IR) (Fig 1) and an increase in expression of fully-spliced FUS transcript (FUS-FS). However, as we do not yet know how FUS-IR is involved in FUS autoregulation, our initial questions were:

1. Where is FUS-IR localised in neurons?
2. What is the rate of degradation of FUS-IR compared to FUS-FS?

2. Methods & statistical analysis
We used primary mixed ventral horn cultures (pVHCs) from wildtype mice embryos for our experiments. We carried out cellular fractionation and fluorescent in-situ hybridisation (FISH) to compare cytoplasmic and nuclear levels of FUS-IR, by

t-test. For our second question, we halted transcription via treatment with ActinomycinD for various timepoints to observe degradation rates of FUS-IR and FUS-FS.

3. Results and conclusions
FUS-IR is localised in the nucleus – there was evidence of an almost complete absence of FUS-IR in the cytoplasm of pVHCs from both cellular fractionation and FISH experiments ($p < 0.5$). FUS-IR had a longer half-life (approx. 3 hours) than would be expected if FUS-IR were immediately degraded in the nucleus (< 30 minutes). FUS-FS initially increased after halting of transcription, which could be explained by FUS-IR being spliced into FUS-FS. To further understand how intron retention in FUS mRNA alters autoregulation, we are conducting further experiments that can clarify whether FUS-IR is eventually spliced into FUS-FS or degraded.

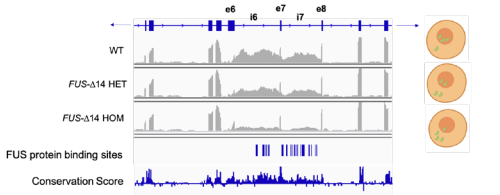

Fig. 1. RNA-sequencing coverage of *FUS* mRNA for wild-type, *FUS*-Δ14 heterozygous and *FUS*-Δ14 homozygous samples from exon 2 to exon 11 of the FUS transcript. Right schematic indicates level of FUS mislocalisation in the sample. The lower panels show FUS iCLIP binding sites and phyloP conservation.

Subcellular distribution of astroglial receptors monitored with super-resolution microscopy

Unique Code: TP001261

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Astrocytes play an active role in shaping and maintaining neuronal circuits. In addition to their long-established role in extracellular potassium buffering and glutamate uptake, these cells can also regulate the activity of local synaptic circuits through secretion and clearance of neurotransmitters. Whilst the molecular signal exchange between astroglia and synapses occurs in a highly heterogeneous microenvironment on the nanoscale, the spatial subcellular distribution of the underlying molecular machineries remains poorly understood.

We employed super-resolution single molecule localisation microscopy (SMLM) to visualise the 3D positions of neurotransmitter receptors and transporters in astrocytes. This imaging technique relies on the sequential activation, imaging and bleaching of a sparse subset of fluorescent molecules. Thus, images can be obtained with sub-diffraction resolution by localising individual activated molecules in each frame.

Approach for statistical analysis
We used t-test to assess the level of significance between two groups and ANOVA with Bonferroni post-hoc test in experiments with more than two groups.

Using SMLM, we were able to localise cytoskeletal proteins as well as clusters of receptors and transporters in astrocytic and neuronal membranes in fixed cultured cells and in brain slices. Moreover, we assessed the positional relationship

between synapses and astroglial receptors and transporters through multi-colour imaging. We determined that astroglial coverage of excitatory synapses is altered in different conditions compatible with long-term synaptic potentiation and depression, providing further evidence for the role of astrocytes in shaping synaptic transmission.

Entorhinal neurons derive from precursors expressing a glial progenitor marker

Unique Code: TP001334

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Oligodendrocyte progenitors (OLPs) continuously generate myelinating oligodendrocytes in the adult brain, but whether OLPs give rise to adult-born neurons remains contentious. To fate-map and study the possible neuronal fate of OLPs, we used a combination of transgenic reporter and knockout mouse lines with immunohistochemistry. The data was analysed using nonparametric one-way analysis of variance (ANOVA) with post-hoc Dunn tests. First, we made a mouse reporter line in which cells expressing platelet-derived growth factor receptor (Pdgfra) – a marker considered to be exclusively expressed in OLPs in the brain – also express Cre under the control of tamoxifen (Pdgfra-CreERT2). After crossing Pdgfra-CreERT2 mice to a yellow fluorescent protein (YFP) reporter line, we identified YFP-expressing layer 2 and 3 projection neurons in the lateral entorhinal cortex (LEC), an object memory-related cortical area in the hippocampal formation. Labelled LEC neurons expressed low levels of doublecortin, a marker for immature and newly differentiated neurons, and exhibited the morphological and molecular characteristics of excitatory projection neurons. Over time post-tamoxifen, there was an accumulation of YFP-labelled LEC neurons (0.7 ± 0.7 neurons/mm2 at +28 days post-tamoxifen to 6.3 ± 0.9 neurons/mm2 at +180 days post-tamoxifen, Kruskal-Wallis one-way ANOVA, $\chi2(2) = 7.2$, $p = 0.0036$); these LEC neurons did not originate from cycling progenitors. Using a membrane-bound green fluorescent protein (mGFP) reporter line, we found that the small population of labelled LEC neurons projected axons to dentate gyrus and CA3, and that the accumulation of LEC neurons correlated with a steady increase in the intensity of mGFP labelling of the perforant path. Importantly, the mGFP-labelled tracts were not due to increased myelination. Combined, these findings indicate that Pdgfra+ postmitotic precursors give rise to an accumulating number of LEC neurons that project to the hippocampus, raising questions about their functional significance.

Psychiatry and mental health

Neurotrophin receptor activation rescues cognitive and synaptic abnormalities caused by hemizygosity of the psychiatric risk gene Cacna1c

Unique Code: TP001042

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Topic: Psychiatry and mental health

Introduction
Human genetic studies have revealed a strong link between alterations in genetic dosage of CACNA1C, encoding the alpha-1 subunit of CaV1.2 L-type voltage-gated calcium channels, and risk for psychiatric disorders including schizophrenia (SZ) and bipolar disorder (BD). In this study we used a Cacna1c+/- rat model in order to map the mechanistic links between reduced CACNA1C dosage and cognitive, synaptic, and circuit phenotypes implicated by patient studies.

Methods
We used Cacna1c+/- rats with a truncating mutation in exon 6 of Cacna1c gene, having ~50% decrease in hippocampal Cacna1c mRNA and protein. We combined behavioural testing of contextual fear conditioning (CFC), in vivo entorhinal-hippocampal network synchronization, ex vivo assays for synaptic plasticity, postsynaptic Ca2+ signalling and excitability of pyramidal neurons, and immunohistochemical assays for ERK and CREB signalling pathways in dorsal CA1 area.

Approach for statistical analysis
Sample sizes were determined based on effect sizes determined from pilot data and published studies. Animals were assigned pseudo-randomly to experimental groups, and experiments performed blind to genotype. Statistical analysis was adapted to account for repeated measures and nested data.

Results and conclusions
Cacna1c+/- rats have marked impairments in latent inhibition of contextual fear conditioning, indicating inability of learning to disregard non-salient stimuli. This behavioural deficit associates dys-coordinated network oscillations during learning, pathway-selective disruption of hippocampal synaptic plasticity, impaired dendritic spine Ca2+ signalling, and decreased Extracellular-signal Regulated Kinase (ERK) pathway signalling. Activation of the ERK pathway with a small molecule TrkB/TrkC neurotrophin receptor agonist rescued the behavioural and synaptic plasticity deficits. These results establish a map between genetic variation in CACNA1C and disruptions in experience-dependent synaptic signalling and circuit activity culminating in cognitive alterations seen in psychiatric disorders. Our findings highlight activation of neurotrophin signalling pathways with BDNF mimetic drugs as a genetically informed therapeutic approach for rescuing behavioural abnormalities in psychiatric

Acute and long-term psychological effects of psychedelics in adolescents: a preliminary prospective study

Unique Code: TP001182
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Topic: Psychiatry and mental health

Introduction – Adolescents (10-24 years old) have exhibited a relatively clear increase in mental illness in recent years. Psychedelics could hold potential as early interventions, shown to induce long-term improvements in psychological outcomes known to be protective of mental illness. However, existing research has not differentiated between younger and older individuals, raising the question of whether adolescents respond differently to acute subjective psychedelic

experiences.

Methods – The study sample consisted of adolescents (N=435; average age 20.4 ± 2.2 years) and adults (N=654; average age 36.5 ± 9.7). Self-reported data including measures on well-being, acute psychedelic experiences and contextual factors were collected via a large-scale prospective online cohort study.

Statistical analysis approach – Descriptive and inferential statistics including correlations, t-tests, analysis of variances, and multiple linear regression models were employed to analyse data, with statistical significance set at $p < 0.05$.

Results – Psychological well-being significantly increased in adolescents two and four weeks following psychedelic use, congruent with observed changes in adults. Acute subjective effects differed between the age groups; adolescents reported significantly higher challenging experiences and ego-dissolution, mediated by self-reported drug dose. The extent of ego-dissolution was a significant positive predictor of well-being increases in adults but showed no predictive significance in adolescents. No specific increases in persisting perceptual changes were observed and aggregate decreases in both suicidal ideation and delusional thinking were seen in the adolescents, with the latter surviving correction for multiple comparisons.

Conclusions - The study provides first known evidence of the potential of psychedelics to be early interventions in adolescent mental health, but also suggests that certain types of experiences known to be beneficial in adults may not be beneficial for younger people. This possible age-related mechanistic disparity may be reflective of a need for ego-stability during adolescent identity formation and should be taken into serious consideration in future trials using psychedelics in adolescent samples.

Structural Covariance Network Changes in Alcohol Dependence

Unique Code: TP001241

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Topic: Psychiatry and mental health

Introduction

Alcohol dependence (AD) is known to be associated with reduced grey matter volume but with partial recovery in abstinence. Studies on volumetric change have typically used whole-brain voxel-based approaches or examined isolated regions of interest. Structural covariance networks instead capture inter-subject covariance of morphology, allowing examination of coordinated degeneration using graph theoretical analysis. Here, we examine group-level network structure to gain new insights into AD neurobiology.

Method

Structural MRI scans were obtained in abstinent individuals with lifetime AD (n=64, 18±43 months abstinent) and a matched control group (n=68). Data were processed using Freesurfer to obtain cortical and subcortical estimates of grey matter volume from 82 regions using the Desikan-Killiany Atlas. Common global and local graph metrics were examined across a range of thresholds. Multi-threshold permutation correction was used to identify group effects. Network

resilience was examined through removal of network nodes using targeted and random attacks. A Bayesian multilevel modelling approach was used to compare regional grey matter volume between groups.

Results
There were no differences in global network properties between groups at any threshold. Nodal analyses highlighted reductions in centrality (closeness and betweenness) in AD. Differences were mostly in temporal and parietal regions and persisted across a range of thresholds. Visual inspection of graphs highlighted reduced edges from affected nodes to subcortical and frontal regions in AUD. Simulated network attacks did not reveal a different pattern of reduction in global efficiency. Multilevel modelling showed small but widespread volume reductions in AUD.

Discussion
Our findings highlight a pattern of nodal disruptions in AUD without global differences in network organisation. However, there was little evidence of atrophy in regional grey matter volume. Results are in agreement with the notion of partial recovery in abstinence, but local network differences could reflect regional variability in neurodegeneration and recovery in relation to AD. Structural covariance networks might be able to detect more subtle aberrations in grey matter than than traditional analyses.

Antidepressant efficacy and monoamine reuptake modulators of herbal origin

Unique Code: TP001254
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Topic: Psychiatry and mental health

Introduction: Adaptogens such as Rhodiola rosea have traditionally been used for centuries and are reported to stimulate concentration and focus, whilst promoting neuroprotective, anti-depressive and anxiolytic effects in patients. Data from animal studies and human clinical trials suggest that it may be effective in monoamine modulation and the treatment of depression, with high tolerance and virtually no side effects. Its adaptogenic activity is believed to be due to action on monoamine and opioid synthesis, transport and receptor activity. Its main bioactive components are reported to be the phenylethanoids p-tyrosol and its glycoside salidroside; phenylpropanoids rosarin, rosavin and rosin; flavonoids, triterpenes, monoterpenes, and phenolic acids. However, commercial Rhodiola extracts are typically standardised to rosavins and salidroside only.

Methods: To test whether Rhodiola modulates neurotransmitters concentration via inhibition of serotonin (SERT) and noradrenaline (NET) transporters, [3H]MPP+ uptake was analysed in two in-vitro neuronal model systems (SH-SY5Y and T-REx-293 SERT cells).

Approach for statistical analysis: One-way ANOVA with Tukey post hoc was used to detect significant differences between treatments.

Results and conclusion: In our test model, tyrosol and rosarin induced significant dose dependent inhibition of NET dependent MPP+ uptake in SH-SY5Y cells. However, when exposed to a commercial Rhodiola extract, more potent inhibition of NET was observed in SH-SY5Y cells. Interestingly, Rhodiola had no effect on SERT dependent uptake in T-

REx-293 SERT cells.

Rhodiola's adaptogenic, antidepressant and anxiolytic activities are thought to be associated with modulation of serotonin and inhibition of monoamine oxidases. These results suggest that the reported effect on attention and focus could be associated with modulation of noradrenaline via NET inhibition only. The higher efficacy of the extract, as compared to isolated constituents, is indicative of additive/synergistic effects, or perhaps the presence of an overlooked potent secondary metabolite. Future research will focus on the component analysis of commercial Rhodiola formulations and the subsequent bioassay of these additional extracts.

Interoceptive functional dysconnectivity is associated with heightened peripheral inflammation in depression

Unique Code: TP001292

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Topic: Psychiatry and mental health

Introduction: Increasing evidence is pointing towards an inflammation-linked subphenotype of major depressive disorder (MDD). Presently, the body of findings substantiating this stratum of depression, so-called inflammation-linked depression, are peripheral correlates i.e. associations between peripheral immune markers and depressive symptoms. Limited clarity has been shed on the neural correlates of inflammation-linked depression. This study aimed to understand the mechanistic brain-immune axis in inflammation-linked depression by investigating associations between network-level functional connectivity (FC) abnormalities and peripheral inflammation in MDD cases. Methods: This investigation was conducted under the Biomarkers in Depression (BioDep) study, by the Wellcome Trust Consortium for the Neuroimmunology of Mood Disorders (NIMA). Resting-state functional magnetic resonance imaging (fMRI) and peripheral blood immune biomarker data (C-reactive protein; CRP, cytokine panel and immune cells) were collected on N=46 healthy controls (HC; CRP <3mg/L) and N=83 cases of MDD, stratified further into low CRP (loCRP MDD; <3 mg/L; N=50) and high CRP (hiCRP MDD; > 3 mg/L; N=33). Network-based statistics (NBS) was firstly performed to test FC difference in HC vs hiCRP MDD. Association between resulting network and peripheral inflammation, indexed by CRP and interleukin-6; IL-6 was then examined in MDD cases only. Approach for statistical analysis: Case-control and within-group comparisons of FC distribution were estimated using two-sample Kolmogorov-Smirnov tests. Correlation between edge-wise FC within NBS network and immune markers were estimated using Pearson's correlation. Sensitivity analyses adjusting for effects of sex and BMI was performed using hierarchical linear regression. Results: NBS testing revealed a single network (primary threshold tprimary=3.8, one-tailed p=0.043) anatomically connecting the insula/frontal operculum and posterior cingulate cortex (PCC). CRP and IL-6 covaried negatively with average network connectivity.

Conclusions: The findings suggest that subgroup of MDD cases with heightened peripheral inflammation exhibit greater dysconnectivity within a brain network related to interoceptive processes.

Effect of Covid-19 Pandemic on Mental Health and Wellbeing during Pregnancy

Unique Code: TP001314

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Topic: Psychiatry and mental health

The COVID-19 pandemic has been shown to cause debilitating long-term consequences regarding mental health. This was evident during previous pandemics and mental health crises. The World Health Organization (WHO) recently highlighted the impact of the Covid-19 pandemic on the psychological status of pregnant females and their newborns. The goal of this study is to assess the impact of the Covid-19 pandemic on mental health among pregnant women specifically anxiety and depression. Data were extracted from electronic databases such as PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) without any custom range of time, language, or keywords. Studies that reported anxiety, depression, or both were included in the study. Data from twenty-five studies with a total of 18,088 pregnant females were recorded and transferred to MedCalc software for statistical analysis. Forest plot was completed and publication bias was evaluated by Egger's test for both anxiety and depression parameters, which resulted in a 95% confidence interval. The risk of bias was evaluated by the Youden plot as well. A comparison of analysis between anxiety and depression was done. All studies reported that there has been a high prevalence of anxiety and depression among pregnant women during the Covid-19 pandemic. It is thus, imperative for healthcare organizations to optimize their perinatal care systems in an effort to minimize the rates of anxiety and depression among pregnant women during the Covid-19 pandemic.

Associations Between Major Psychiatric Disorder Polygenic Risk Scores and Blood-Based Markers in UK Biobank

Unique Code: TP001337

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Topic: Psychiatry and mental health

Introduction

Major depressive disorder (MDD), schizophrenia (SCZ), and bipolar disorder (BD) have both shared and discrete genetic risk factors and abnormalities in blood-based measures of inflammation and blood-brain barrier (BBB) permeability. The relationships between such genetic architectures and blood-based markers are however unclear.

Methods

We investigated relationships between polygenic risk scores for these disorders and peripheral biomarkers in the UK Biobank cohort. We calculated polygenic risk scores (PRS) for samples of n = 367,329 (MDD PRS), n = 366,465 (SCZ PRS), and n = 366,383 (BD PRS) individuals from the UK Biobank cohort. We examined associations between each disorder PRS

and 58 blood markers, using two generalized linear regression models: 'minimally adjusted' controlling for variables including age and sex, and 'fully adjusted' including additional lifestyle covariates such as alcohol and smoking status.

Approach for Statistical Analysis
Multiple testing correction was applied to all tests conducted across all traits using the Bonferroni multiple comparison test. Significant associations were determined using a threshold of pcorr < .05.

Results and Conclusions
In total, 15/58, 14/58 and 10/58 peripheral markers were significantly associated with MDD, SCZ and BD PRS respectively for both models. Many were disorder-specific, with 10/15 MDD PRS associations unique to MDD. Moreover, several of these disorder-specific associations for MDD and SCZ were with immune-related parameters, with mostly positive and negative associations identified for MDD and SCZ PRS respectively.

This study suggests that MDD, SCZ and BD have shared and distinct peripheral markers associated with disorder-specific genetic risk. The results also implicate inflammatory dysfunction in MDD and SCZ, albeit with differences in patterns between the two conditions, and enrich our understanding of potential underlying pathophysiological mechanisms in major psychiatric disorders.

Distinct white matter differences in young adolescents with psychotic experiences: along tract analysis of contiguous segments of the cingulum bundle

Unique Code: TP001349

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Topic: Psychiatry and mental health

Introduction
The cingulum is a white matter tract lying underneath the cingulate cortex, connecting frontal, parietal and medial temporal regions and a role has been suggested in psychosis. Few studies have found robust differences in either psychosis or the extended psychosis phenotype, possibly due to the heterogeneous nature of the tract. We hypothesize that differences may exist along the cingulum bundle rather than as a unitary structure in adolescents with psychotic experiences (PEs).

Methods
25 young people with PEs (11-13 years) and 25 matched controls were recruited from the Adolescent Brain Development study. Participants underwent high angular resolution diffusion MRI. Following pre-processing, whole brain tractography was performed using constrained spherical deconvolution. Four cingulum sections (subgenual, body, retrosplenial and parahippocampal) were reconstructed by two independent raters using an anatomical protocol.

Volumes and diffusion metrics [fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD)] were calculated. Each aforementioned section was also subdivided along its length allowing 'along tract' diffusion resampling, at each subdivided segment.

Approach for statistical analysis
Extracted diffusion metrics were inspected to identify and remove outliers. All comparisons were performed for each hemisphere independently. One-way ANCOVAs controlling for age, sex and estimated total intracranial volume were performed separately for the volumes and diffusion metrics of each of the four sections bilaterally. Multiple comparisons were corrected with Bonferroni correction.

Results and conclusions
No differences in volume or diffusion metrics between groups were found at the level of the four cingulum sections. Along tract analysis of the sections revealed diffusion differences along contiguous segments of the left retrosplenial and right subgenual sections. FA increases were found in contiguous segments of the anterior left retrosplenial and anterior right subgenual sections and decreases were found in posterior contiguous segments of the same regions. These findings suggest distinctive neuronal changes along these contiguous segments in PE compared to control. Funded by a ERC (MC).

The Cerebellar Peduncles in Adolescents with Psychotic Experiences: A DTI Investigation

Unique Code: TP001350
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Topic: Psychiatry and mental health

Introduction
The role of the cerebellar peduncles, the main input and output tracts of the cerebellum, in motor function has long been appreciated. More recently, their importance in cognitive and emotional function and psychiatric conditions has come to light. Due to this, and the motor problems associated with psychosis, we conducted a neuroimaging evaluation of the cerebellar peduncles in youths at risk of psychosis compared to controls.

Methods
Participants were recruited as part of the Adolescent Brain Development Study. Psychotic experiences (PE) were determined using a 7-item Adolescent Psychotic-Like Symptom Screener (APSS) and the Schedule for Affective Disorders and Schizophrenia for School-aged Children, Present and Lifetime Versions (K-SADS). Participants underwent DTI imaging at 2 time points, approximately 5 years apart. The peduncles were isolated using Explore DTI following an anatomical protocol.

Approach for Statistical analysis
IBM SPSS Statistics 26 was used for all statistical analyses. Analyses of covariance were performed to compare the

diffusion data in each of the cerebellar peduncles between healthy participants and patients with psychotic experiences (PE). Additionally, paired T testing was performed to elucidate potential differences between the two time points that the data was collected at. Age, sex and total intracranial volume were corrected throughout the analysis.

Results and Conclusion
In total 16 participants with PEs and 17 controls were included. The mean age was 15 and 20 at time points 1 and 2 respectively. Our study found no significant differences in the peduncles (superior, middle or inferior) between PE and controls at either time point. Our findings suggest that the cerebellar peduncles are not implicated in the pathogenesis of psychotic experiences in adolescents. Motor symptoms may be due to alternative structures such as the cerebellum itself. However, we cannot rule out a potential role for the cerebellar peduncles in the progression of adolescent psychotic experiences as our sample size was quite small and DTI has some inherent limitations. Future studies must include larger samples assessed at more time points, adverse childhood experiences, and aligned brain structures.
Funded by ERC grant (MC).

Hippocampal CA1 involvement in psychosis independent of diagnosis: A systematic review of hippocampal subfields

Unique Code: TP001353
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Topic: Psychiatry and mental health

Introduction:
Psychosis is a broad term encompassing problems in reality testing. It presents across many psychiatric conditions such as schizophrenia but also in other disorders such as mood disorders. The hippocampus in the medial temporal lobe has shown consistent involvement across the psychosis spectrum. Recent advances in MRI allow imaging of the smaller functional hippocampal substructures. Although there have been disorder-specific reviews of hippocampal substructures in psychosis, no study to date has focused on substructures in psychosis independent of diagnosis.

Methods:
PubMed, Google Scholar, MEDLINE and EMBASE were searched using the terms: (Hippocampus AND psychosis) OR (Hippocampal subfield AND psychosis) OR (Subiculum AND psychosis) OR (Cornu ammonis AND psychosis) OR (dentate AND psychosis). References from articles were checked, extracted and incorporated as required.

Approach for statistical analysis:
Risk of bias was assessed using the Cochrane Risk of Bias tool.
Results and conclusions:

16 studies examined hippocampal subfields in psychosis. 15 studies identified reductions in CA1 volumes. CA2/3 and CA4/DG reductions were found in 8 studies each, with subiculum, presubiculum, molecular layer and fimbria

involvement in 7, 4, 3 and 2 studies respectively. Many studies also recognised neighbouring amygdala and parahippocampal regions. The most commonly studied psychotic condition was schizophrenia, with bipolar depression being the second most common. CA1 was the most common hippocampal substructure impacted across the psychosis spectrum, with its adjacent subfields on either side (CA2/3 and dentate/CA4) also affected. CA1 is involved in autobiographical memory and also enables the re-integration of distinct but related memories previously separated earlier in the hippocampal circuitry. Unpairing or mispairing of linked memories signals may underlie the core symptoms of psychosis. This research hints at the possibility of the hippocampal CA1 substructures as a biomarker for psychosis, independent of diagnosis. A full meta-analysis of the data is underway. Funded by a European Research Council Consolidator Award to MC (iHEAR 724809)

Socioeconomic Status and Depression: A Systematic Review and Meta-Analysis

Unique Code: TP001388

Authors: Anders Jespersen - Centre for Clinical Brain Sciences University of Edinburgh, Rebecca Madden - Centre for Clinical Brain Sciences University of Edinburgh, Heather Whalley - Centre for Clinical Brain Sciences University of Edinburgh, Andrew McIntosh - Centre for Clinical Brain Sciences University of Edinburgh

Topic: Psychiatry and mental health

Several studies have linked measures of socioeconomic deprivation to happiness and wellbeing, but in part due to narrow inclusion criteria its relationship to clinical depression and the generalisability of findings remains unclear. This systematic review aims to investigate the association between clinical depression and socioeconomic status incorporating studies from low- to high-income countries across a wide geographical and temporal sampling frame.

Included studies investigated the association between clinical depression and socio-economic status (SES). Depression was diagnosed according to any recognised diagnostic criteria, using self-reported symptoms elicited by an interviewer and structured instrument, or by self-reported questionnaire. We also included studies that derived diagnoses from routinely collected linked health record data.

Education (duration or attainment), household income, and/or occupation were used as measures of SES. Literature searches were conducted in PsycINFO, EMBASE, MEDLINE, Web of Science and ASSIA, with no restrictions on publication date or country of origin. All searches (except for Web of Science) were conducted using expanded subject headings.

In total, N=7,943 studies were screened against title and abstract, N=521 studies were full text screened and N=137 studies were included in the systematic review. Of those studies N=59 reported data suitable for meta-analysis. The total sample size of those N=59 studies was N=204,465 people with N=13,796 depression cases from 28 countries.

We found a significant association between low SES (OR = 1.7, 95% CI = 1.2; 2.4), low educational attainment (OR = 1.5, 95% CI = 1.1; 2.1), low income (OR = 1.9, 95% CI = 1.2; 3.2), unemployment (OR = 1.6745, 95% CI = 1.3; 2.1) and increased risk of depression.

This systematic review highlights the relatively strong association between low SES and risk of depression across diverse cultural, geographical, and economic contexts.

These findings will have implications for both research and policy making and necessitate further studies to address the

nature and mechanisms of any causal associations. While the studies were highly heterogeneous, the large sample size and diversity of contexts increases confidence in our study.

Power signatures of neuronal recordings from habenula in depressive patients predict their severity

Unique Code: TP001393

Authors: Saurabh Sonkusare - Department of Psychiatry University of Cambridge,

Topic: Psychiatry and mental health

Introduction

Major depressive disorder affects approximately 2% of the world's population. Effective treatment strategies to complete resolution of all symptoms are still elusive. Deep brain stimulation (DBS) targeting habenula have shown positive results in ameliorating symptoms. However, the neuronal recordings from this region, either spontaneous (resting state) or task induced, have not been investigated which may provide complimentary information for DBS evaluation in depression. Here, we acquired neuronal recordings from habenula resting state and during an emotion picture viewing task from patients undergoing DBS surgery.

Methods

We first characterise the resting power profile, specifically aperiodic component (1\f slope), physiologically interpreted to signify neuronal spiking. We show that this aperiodic exponent of the left habenula, from resting as well as an emotional task data, predicts depression severity. Furthermore, we also evaluate picture stimuli induced responses with time-frequency (TF) decompositions. Finally, we also investigate habenula connectivity with prefrontal cortex activity (measured with scalp EEG) via time varying coherence analysis.

Approach for statistical analysis

We compared aperiodic component between rest and task with paired t-test and correlation analysis. Condition differences in TF task responses were statistically tested with permutation testing. Time varying coherence between conditions for habenula-prefrontal connectivity were also tested with permutation testing.

Results and conclusions

We found that the aperiodic component of the left habenula was strongly correlated between rest and task. This aperiodic component, a measure of neuronal spiking also showed significant positive correlation with depression severity. The task TF responses showed time locked responses with condition difference at around 1s with significantly decreased activity for negative valence stimuli. Eventually we also show increased synchrony between habenula and prefrontal cortex in alpha frequency range for positive stimuli when compared to negative stimuli. Our results thus provide direct evidence of habenula’s activity in depression and which may inform clinicians for refining DBS protocols in a personalised manner.

Sensory and motor systems

Face and limb movements in very pre-term human infants

Unique Code: TP001072

Authors: Kimberley Whitehead - Neuroscience, Physiology and Pharmacology University College London, Neelum Mistry - Neuroscience, Physiology and Pharmacology University College London, Tuomas Koskela - Research IT Services University College London, Mohammed Rupawala - Neuroscience, Physiology and Pharmacology University College London, Judith Meek - Elizabeth Garrett Anderson Wing University College London Hospitals, Lorenzo Fabrizi - Neuroscience, Physiology and Pharmacology University College London, James C Dooley - Department of Psychological & Brain Sciences University of Iowa, Mark S Blumberg - Department of Psychological & Brain Sciences University of Iowa

Topic: Sensory and motor systems

Introduction

In neonatal rats, movements of the whiskers and limbs occur profusely during sleep, follow a stereotyped phenotype (e.g. rapid displacement of the whisker followed by a slower return to a new baseline position) (Dooley et al. 2020, Nasretdinov et al. 2020)), and may be required for typical sensorimotor development. Here we examined whether similarly stereotyped motor activity occurs frequently during sleep in very pre-term human infants.

Methods

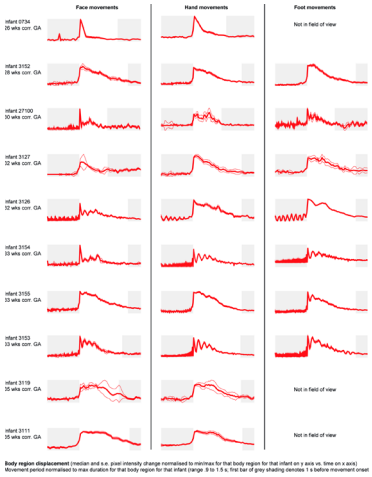
Subjects comprised 10 very pre-term infants (born 24-32 weeks gestational age (GA)). Between 26-35 weeks corrected GA, we acquired video recordings at ≥25 frames per second while they slept.

To quantify movements, we used custom-written MATLAB code to detect frame-by-frame changes in pixel intensity within regions-of-interest (ROI) (face or limbs), adjusting for changes in pixel intensity within a control ROI to avoid lighting fluctuations being erroneously detected as movement. Movement onsets for each ROI were defined as exceeding a threshold equal to the mean value across all frames plus 3 standard deviations. Movements that were separated by less than 0.1 sec were combined. Movement periods were defined as ending 0.5 sec after pixel intensity change decreased below threshold, up to a maximum duration of 1.5 sec.

Results and conclusions

Movements occurred frequently during sleep at a median rate of 234 per hour for the face (interquartile range (IQR): 175-342), 127 per hour for the hand (IQR: 104-357), and 135 per hour for the foot (IQR: 89-214). Movements followed a relatively stereotyped temporal trajectory, with sharp initial displacement of the body region followed by a slower 'resettling' to its new position (Figure). While the frequency of movements did not change with age, the mean duration of face and hand movements increased with corrected GA (face: $r = .754$, $p = .012$; hand: $r = .663$, $p = .037$; Spearman's correlations).

Stereotyped motor activity occurs frequently during sleep in very pre-term human infants, and could serve a developmental role. Future work in a larger cohort will examine how these movements modulate ongoing cortical activity, and whether this predicts later sensorimotor functioning.



Endogenous cortical activation elicits refractoriness to external stimuli in pre-term infants

Unique Code: TP001073

Authors: Kimberley Whitehead - Neuroscience, Physiology and Pharmacology University College London, Mohammed Rupawala - Neuroscience, Physiology and Pharmacology University College London, Maria Pureza Laudiano-Dray - Neuroscience, Physiology and Pharmacology University College London, Judith Meek - Elizabeth Garrett Anderson Wing University College London Hospitals, Sofia Olhede - Department of Mathematics Ecole Polytechnique Federale de Lausanne, Lorenzo Fabrizi - Neuroscience, Physiology and Pharmacology University College London,

Topic: Sensory and motor systems

Introduction

Developing sensory neuronal networks fire spontaneously in preparation to receiving external input. Pre-term EEG is characterised by high amplitude activity bursts with discrete voltage distributions across the scalp. Bursts can also be elicited with external stimuli such as noise and touch. While sensory evoked bursts may have voltage distributions similar to those that occur spontaneously, it is not clear whether they involve the same underlying cortical networks. To answer this question, we took advantage of network refractoriness, i.e. that spontaneous activation is followed by a period when the system cannot respond to further input.

Methods

We recorded EEG in response to mechanical taps of hands and feet in 35 healthy infants of median 32 weeks corrected gestational age (CGA; range 28-35 weeks) and postnatal age (PNA) 7 days. (CGA = gestational age + PNA) We then assessed how magnitude and distribution of endogenous activity preceding the stimulus affected the response to the tap.

Results and conclusions

Somatosensory stimulation evoked significant energy changes in the delta, alpha-beta and gamma bands with peak changes of 6 dB at 1Hz (delta) and 13Hz (alpha-beta). Energy changes at lower frequencies were more widespread across the scalp than those at higher frequencies, which instead were localised at the somatotopic representation of the stimulated limb (i.e. central-contralateral for the hands and central-midline for the feet).

The energy changes evoked by tapping the limbs in each band were inversely related to the energy present before the stimulus (baseline) and to how similar its distribution was to that of the somatosensory evoked response (SIM) ($p <$

.0001 after correcting for CGA; multiple linear model used: energy change = b0 + b1 CGA + b2 baseline + b3 SIM + e; adjusted whole model r squared = 0.54 (delta), 0.50 (alpha-beta) and 0.27 (gamma)).

These results indicate that ongoing spontaneous activity makes the brain refractory to an incoming external stimulus which tries to engage the same network. These results are supportive that spontaneous activity in the pre-term period represents the activation of maturing sensory cortical architectures in preparation to engagement with the external environment.

VISUAL ADAPTATION ACROSS THE OPTIC TECTUM IN LATE-STAGE ZEBRAFISH LARVAE

Unique Code: TP001080

Authors: Sandra Toledo-Rivera - Biomedical Sciences The University of Sheffield, Anton Nikolaev - BMS The University of Sheffield, Elliot Birkett - BMS The University of Sheffield,

Topic: Sensory and motor systems

Adaptation is a fundamental property of any sensory system. In the visual system, the retina is the primary source of this property and the mechanisms are largely characterised, with bipolar and ganglion cells being the primary visual adaptation source. However, much less is known about the mechanisms and function of this downstream of the retina (higher brain function level).

Here, we used 2-photon in vivo imaging and patch-clamping recordings to look at the activity of retinotectal projections and tectal neurons of late-stage larvae zebrafish (12-21days postfertilization) along with calcium indicators expressed pan-neuronally (NBT:GCaMP3 and Huc:GCaMP6). After a combination of voxel-wise analysis, manual sorting and statistics using custom-made Igor Pro scripts and Graphpad Prism, we show that the optic tectum exhibits a profound adaptation to different types of visual stimuli and the degree of this depends on the stimulus strength and type (n=16,421 traces from 12 fish).

We found that the adaptation was particularly strong in the stratum album centrale and stratum griseum centrale in the contralateral tectum and the ipsilateral tectum. Thus, there is an additional source of adaptation originating within the tectum. This makes the visual responses in the output areas adapt nearly completely after the first presentation of the stimulus. Additionally, we demonstrate that other areas of zebrafish brain exhibit different degrees of visual adaptation: The optic tectum and pretectum exhibit strong depression, whereas telencephalon, both habenulae and the hindbrain exhibit weak adaptation or even facilitation.

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Neuromodulation in auditory thalamus upon associative learning

Unique Code: TP001099
Authors: Joana Amorim Freire - Department of Biomedicine University of Basel,
Topic: Sensory and motor systems

Associative learning links sensory, predictive stimuli from the environment with their outcomes and depends on reliable integration of sensory inputs to shape behavioral adaptations and ensure an animal's survival. Several cortical and limbic brain areas have been identified as sites for associative learning. However, the role of thalamic structures that process, relay and store associative learning-related sensory information remains largely unknown. The medial geniculate body (MGB), or auditory thalamus, is a site of convergence for auditory as well as somatosensory information. It receives feedforward sensory as well as neuromodulatory input, e.g. acetylcholine - a key component in promoting learning. One prominent cholinergic input to MGB originates in the pedunculopontine tegmental nucleus (PPT). However, the role of brainstem cholinergic inputs to MGB during associative learning remains unknown.

Here we use a combination of deep brain calcium imaging techniques (optical fibres, miniaturized microscopes) as well as optogenetics to unravel the functional role of cholinergic projections in MGB during associative fear learning in freely moving ChAT-cre mice.

We used different non-parametric statistical tests: Wilcoxon sing rank test, to compare the activity of sensory responsive cells during intermingled optogenetic-modulated tone/shock presentations; Kruskal Wallis and multiple comparisons tests, to assess the difference in freezing levels between groups of animals during different optogenetic modulation protocols (i.e. activation and inhibition of PPT-ACh inputs) in a fear conditioning paradigm.

We find that cholinergic projections from the brainstem modulate sensory responses of MGB neurons during fear conditioning. Furthermore, optogenetic manipulation of cholinergic PPT inputs in MGB during fear acquisition affects learning. Our study identifies a role of brainstem cholinergic inputs in multimodal sensory integration during fear conditioning in auditory thalamus. This will broaden our view on how neuromodulators contribute to associative learning in thalamic areas.

Local heterogeneity of sensorimotor representations in cerebellar molecular layer interneuron populations during voluntary whisking

Unique Code: TP001121
Authors: Elisabeth M. M. Meyer - PPN University of Bristol, Paul Chadderton - PPN University of Bristol
Topic: Sensory and motor systems

Mice use their whiskers to actively explore and gather information about their environment. The cerebellum plays a key role in sensorimotor processing during whisking, integrating sensory and motor information from a multitude of brain regions. Within cerebellar cortex, molecular layer interneurons (MLIs) and Purkinje cells (PCs) receive excitatory signals from cerebellar granule cells and local inhibition from MLI networks. MLIs play a key role in determining cerebellar output as they are the exclusive provider of inhibition to PC dendrites and somata. Previously we have shown kinematic whisker signals are linearly encoded in PCs and MLIs during free whisking in individual neurons, but the role of MLI populations in the coding of behaviourally relevant features during active whisking remains elusive.

Here we have used 2-photon calcium imaging in adult head fixed nNos-Cre mice expressing Cre-dependent GCamp6f to measure activity patterns within MLI populations during spontaneous whisking. Wilcoxon signed-rank test was used to compare evoked calcium responses between different whisking conditions. Spontaneous whisking modulated calcium activity of the MLI population in a diverse manner. Individual MLIs exhibiting whisker-evoked activity and located within the same field of view (500um x 500 um) showed varying degrees of whisker angle tuning to similar angles. Upon touching a pole during voluntary whisking, calcium activity of tuned MLIs appeared further increased, and a distortion in the tuning curves compared to obstacle-free whisking was observed. Interestingly, no obvious clustering of MLIs with similar tuning strength could be found. Rather, strongly tuned neurons appear interspersed with non-tuned/non-responsive neurons suggesting functional MLI subnetworks exist within local regions of the cerebellum. Further analysis of the relative locations of concurrently active MLIs will yield important insights into the underlying connectivity rules of the MLI population.

Investigating phase synchrony between sensorimotor cortices while learning a novel bimanual motor learning task

Unique Code: TP001170

Authors: Marleen Schoenfeld - Nuffield Department of Clinical Neuroscience University of Oxford, Charlotte Stagg - Nuffield Department of Clinical Neuroscience University of Oxford, Catharina Zich - Nuffield Department of Clinical Neuroscience University of Oxford

Topic: Sensory and motor systems

Our understanding of bimanual motor learning and its underlying neurophysiological mechanisms is sparse. Therefore, we aim to 1) characterize learning-related changes of different levels of bimanual interaction and 2) investigate if tACS modulates these learning-related changes.

First (study1), we tested the novel bimanual motor learning task in 40 right-handed healthy participants (mean age=25.3years), Fig1A. Participants used two force-grip devices to move a cursor along a path of different angles, Fig.1B. Each hand controlled either the horizontal or vertical movement of the cursor. The different angles resulted in different levels of bimanual interaction, i.e. unimanual(Uni,0°,90°), bimanual with equal force(Bieq,45°) and bimanual with unequal force(Biuneq,22.5°,67.5°).

Second (study2), we explored the effect of phase-synchrony between the left and right sensorimotor cortex using tACS at the individual's beta peak frequency. We performed a one-session between-subject, double-blind study with 54 healthy right-handed participants (mean age=24.05years). TACS was applied with a four-electrode-montage (both M1, both shoulders) for 20min of 2mA peak-to-peak amplitude. Participants either received sham(10s ramp-up and down), in-phase(0°phase-shift), or anti-phase(90°phase-shift) tACS, Fig.1C.

Study1 demonstrated distinct levels of bimanual interaction, Fig2. Two repeated-measures 2x3 ANOVAs were conducted, once with movement time and once with error. Both time (movement time:F1,39=68.61,p=.001,n2p=.64;error:F1,39=81.55,p=.001,n2p=.68) and level (movement time:F2,78=52.53,p=.001,n2p=.57;error:F2,78=1460.82,p=.001,n2p=.97), as well as their interaction was significant(movement time:F2,78=27.13,p=.001,n2p= 41;error:F2,78=13.44,p=.001,n2p=.26). Study 2 replicated these findings, however against our expectations our results suggested no main effect or interaction with beta tACS, Fig3.

The novel bimanual motor task allows to characterise bimanual motor learning with different levels of bimanual interaction. This could be replicated in an independent sample. The underlying neurophysiological mechanisms should be further investigated in real-time, e.g. with Magnetoencephalography. Ultimately, this informs future studies in health and disease to aid motor recovery.

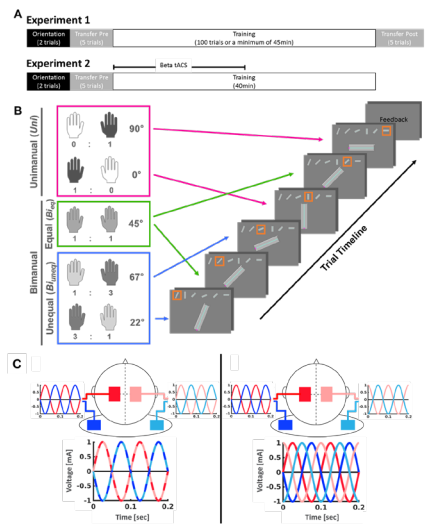

Fig. 1. Schematic overview of experimental timeline (A) and design of the novel task (B) and beta tACS (C).

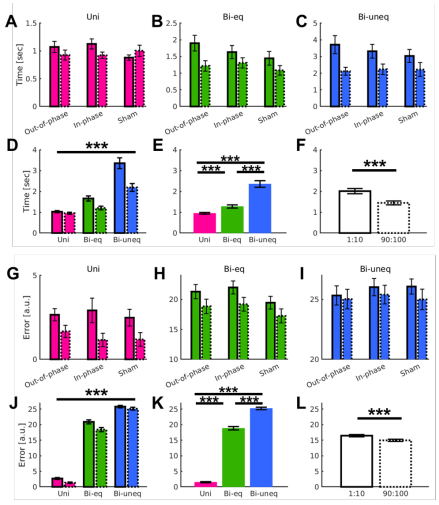

Fig. 2. Results of study 2 for movement time (A-F) and error (G-L) replicate the findings of study 1.

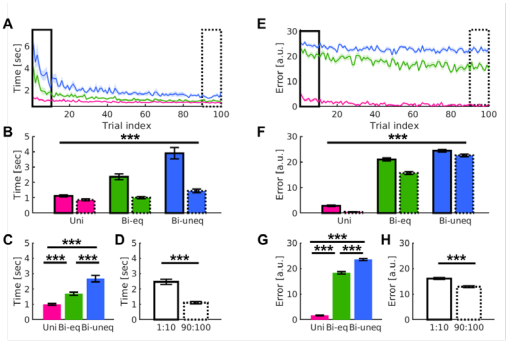

Fig. 2. Results of study 1 for movement time (A-D) and error (E-H) show distinct levels of bimanual interaction.

The Role of Amacrine Cells in Zebrafish Color Vision

Unique Code: TP001222

Authors: Xinwei Wang - School of Life Science University of Sussex,

Topic: Sensory and motor systems

Introduction

In vertebrate retina, bipolar cells (BCs) relay information from photoreceptors to ganglion cells (RGCs). In this pathway, inhibitory interneurons called amacrine cells (ACs) shapes both BC and RGC responses. However, the function of AC populations remains poorly understood. Here, we leverage the tetrachromatic retina of larval zebrafish to probe the role of ACs in spectral processing.

Methods

7-9 days post fertilization larval zebrafish expressing GCaMPs in either ACs or BCs were imaged by multiphoton microscopy during presentation of widefield stimulation from four LEDs spectrally aligned with the peak sensitivities of

the zebrafish's four cone photoreceptors. We imaged signals from BCs and ACs in the intact circuit, as well as from BCs during pharmacological blockage of inhibitory transmission.

Approach for statistical analysis
Data analysis was performed using IGOR Pro 8.0 and MATLAB r2019a.

Results and conclusions
Imaging ACs in vivo revealed a high diversity of spectral signals neatly organised into specific layers of the IPL. Overall, ACs exhibited a dominance of long-wavelength Off-circuits nasally, but a UV-dominance in the acute zone [1].

Imaging BCs before and after pharmacological blockage of AC actions we find: 1) Blocking ACs reliably disinhibits BCs to yield high-amplitude and strongly adapting BC responses; 2) ACs suppress short-wavelength BC responses more strongly than long wavelength BCs; 3) ACs do not tend to invert the polarity of BCs rather they mould the relative weighting of spectral inputs in a generally sign-conserving manner; 4) Even though AC inputs have profound impact on all of BC terminals, the population properties for spectral coding in BCs remains surprisingly constant following AC blockage. It appears that when a function is removed in one set of BCs it is instead unveiled in another. These results suggest that the primary function of ACs in the zebrafish retina is not to dictate spectral processing, but rather to preserve it despite shaping other key properties of the visual response, such as kinetics and amplitudes.

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Whisker movements are affected in the 3xTg-AD mouse model of Alzheimer's Disease

Unique Code: TP001224
Authors: Ugne Simanaviciute - Department of Natural Sciences Manchester Metropolitan University, Richard Brown - Department of Psychology and Neuroscience Dalhousie University, Aimee Wong - Department of Psychology and Neuroscience Dalhousie University, Emre Fertan - Department of Chemistry Cambridge University, Robyn Grant - Department of Natural Science Manchester Metropolitan University
Topic: Sensory and motor systems

Alzheimer's Disease (AD) is the most frequent form of dementia in elderly people. The triple transgenic (3xTg-AD) mouse model of AD is popular in biomedical research as the mice develop both neural and behavioural phenotypes. However, their behavioural phenotype is variable, with findings depending on the specific task, as well as the age and sex of the mice. Whisker movements have been found to robustly reveal motor deficits, as well as sensory and cognitive deficits in mouse models of neurodegenerative disease. Therefore, we examined whisker movements in 3, 12.5 and 17 month female 3xTg-AD mice and their B6129S/F2 wildtype controls. Mice were filmed using a high-speed video camera (500 fps) in an open arena during a novel object exploration task. Qualitative scores of whisking behaviours were analysed by a Kruskal-Wallis test with Dunn's post-hoc. A Linear Mixed-Effects Model with Satterthwaite's method was used to analyse the effect of age and genotype on all the quantitative whisker variables. Results were presented as an ANOVA of the Linear Mixed-Effect Models. Age and genotype effects were found in mice exploring the arena prior to object contact. Specifically, differences in whisker angles and amplitude showed a clear motor phenotype in 3xTg-AD mice at 3 months. Furthermore, qualitative scoring showed differences in whisking in 3xTg-AD mice from 12.5 months. During object contact with their whiskers, 3xTg-AD mice did not reduce whisker spread as frequently as their wildtype controls

at 12.5 months, and whisker amplitude was also affected at 12.5 months, which suggests a sensory or attentional deficit in 3xTg-AD mice at this age. We show that whisker movements are a suitable measure for quantifying genotype and age effects in 3xTg-AD mice. We suggest that whisker movements are a powerful behavioural measurement tool, with particular benefits in capturing behavioural deficits in mouse models that reveal complex or subtle phenotypes, such as in the 3xTg-AD mouse model.

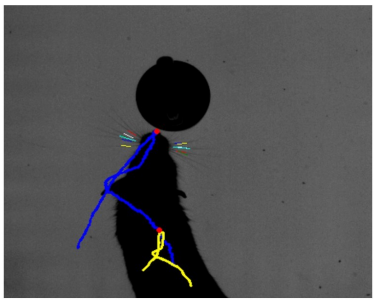


Fig. 1. Example video still of the 12.5 month transgenic mouse. ARTv2 LocoWhisk software was used to automatically locate the mouse centroid (red point, yellow line), nose tip (red point, blue line) and whiskers (coloured lines) on a frame-by-frame basis.

Thalamocortical plasticity mediates GABAergic inhibition for perceptual learning

Unique Code: TP001227

Authors: Joseph Ziminski - Psychology University of Cambridge, Polytimi Frangou - Psychology University of Cambridge, Vasileios Karlaftis - Psychology University of Cambridge, Zoe Kourtzi - Psychology University of Cambridge

Topic: Sensory and motor systems

Introduction: Learning to detect objects in cluttered scenes is a vital skill when interacting with our environment. For example, when crossing a road, we must rapidly identify an oncoming car within the background of a busy street. Humans quickly learn to detect targets from cluttered backgrounds; yet, the brain plasticity mechanisms that support this perceptual learning remain largely unknown. Here we investigate the role of myelination and GABAergic inhibition processes in learning-dependent plasticity.

Methods: We trained human participants in a signal-in-noise detection task that involved discriminating ‘radial’ vs. ‘concentric’ Glass patterns formed of orientated dipoles embedded in noise. We used MPM (multi-parameter mapping) to measure magnetisation transfer (MT) as an indicator of myelin, MRS (magnetic resonance spectroscopy) to measure GABA in occipital-temporal (OCT) cortex, and rs-fMRI (resting state fMRI) to measure functional connectivity. We tested participants at baseline, before (pre-training scan) and after (post-training scan) three training sessions.

Statistical analysis: GLM in SPM12, Pearson’s correlation. p-value <0.05 was considered statistically significant.

Results and conclusions: Following training, MT was significantly increased in the pulvinar, a key visual-thalamic region involved in attentional and salience processing. This MT change correlated with behavioural improvement in the signal-in-noise task, suggesting learning-dependent pulvinar myelination relates to perceptual learning. Further, visual cortex GABA change across training correlated with behavioural improvement, consistent with decreased GABAergic inhibition for learning-dependent plasticity. Interestingly, visual cortex – pulvinar functional connectivity and pulvinar MT changes across training were correlated, suggesting activation-dependent myelination for perceptual learning. Finally, changes

in thalamo-cortical connectivity related to behavioural improvement and visual cortex GABA change, suggesting a key role of thalamocortical connectivity for learning-dependent visual cortex GABAergic plasticity.

Our findings suggest attentional thalamic mechanisms interact with gain control processes in sensory areas for improved perceptual judgements due to training.

Combined slice-specific z-shim and selective field-of-view sequence for spinal cord resting state fMRI: Best of both?

Unique Code: TP001265

Authors: Samantha Mitchell - Psychology Cardiff University, Andrew Lawrence - Psychology Cardiff University, Ronald Hartley-Davies - Clinical Sciences University of Bristol, Jonathan C.W. Brooks - Psychology University of East Anglia, George Tackley - Psychology Cardiff University,

Topic: Sensory and motor systems

Introduction

Resting-state fMRI studies in humans have found functional networks in spinal cord (SC) grey-matter. In SC fMRI, the inhomogeneous magnetic field along the cord, due to the differing magnetic susceptibilities of the surrounding tissues, causes significant signal dropout and distortion. A slice-specific z-shim, originally proposed by Finsterbusch et al. (2012), uses compensatory moments applied in the z-direction and is commonly implemented to reduce this periodic signal dropout. Another technique, selective field-of-view imaging, is also credited with reducing susceptibility artefacts and is also used in SC imaging. The present study aimed to validate the use of the slice-specific z-shim, in conjunction with a selective field-of-view sequence (Siemens ZOOMit), for SC resting state (RS) fMRI acquisitions.

Methods

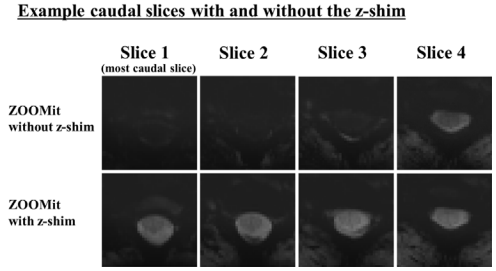
Five adult participants (3 female) completed RS fMRI scans (T2* weighted ZOOMit echo-planar imaging sequence) with and without the z-shim (manually calibrated z-shims). Scans were performed at 3T (Siemens PRISMA; 64-channel head and neck coil). Images were motion corrected using AFNI and pre-processed in Spinal Cord Toolbox (SCT). Automated segmentation performance, mean BOLD signal intensity, temporal signal-to-noise ratio (tSNR), the number of unusable slices, and RS functional connectivity were used to evaluate our aim.

Approach for Statistical Analysis

L1-regularised partial correlations were calculated between SC regions of interest timeseries using FSLNETS and assessed with single-sample permutation-based t-tests (Randomise). Statistical comparisons were conducted using Aligned Rank Transformation ANOVAs and permutation t-tests in R.

Results and Conclusions

As expected, the z-shimmed ZOOMit SC functional images were visibly superior to the ZOOMit SC functional images acquired without the z-shim (see figure). The z-shim resulted in fewer unusable slices, reduced between-slice mean BOLD signal intensity variance and improved SCT automated segmentation precision. Also, with the z-shim, we found additional significant functional connectivity patterns not previously noted in the human literature. Surprisingly however, we did not find significant evidence that the z-shim improved overall mean BOLD signal intensity or tSNR.



A single, clinically relevant dose of baclofen significantly impairs motor sequence learning

Unique Code: TP001271

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Topic: Sensory and motor systems

Introduction

Gaining a new motor skill is an essential process that occurs in everyone's life, from learning how to reach or grab to executing complex motor activities, like writing or dancing. Motor learning is associated with a decrease in the levels of γ-aminobutyric acid (GABA) in the primary motor cortex (Kolasinski and Hinson, 2019). Decreases in GABA levels are also shown to significantly correlate with improved motor learning (Stagg et al, 2011). Modulating GABAergic inhibition may therefore represent an important way to influence this process. Here, we investigated whether increasing GABAergic activity via the GABAB-receptor agonist baclofen would significantly impair motor learning.

Methods and data analysis

We conducted a within-subject, double-blind, placebo-controlled, crossover study to evaluate the effect of a single dose of 20 mg of baclofen on motor learning and brain chemistry. Eighteen young, healthy volunteers came for two sessions, one on which they took baclofen and one placebo. During each session, participants performed a serial reaction time task (SRTT). Functional MRI (fMRI) data was acquired during SRTT and at rest. Magnetic Resonance Spectroscopy Imaging (MRSI) data was also acquired from the left and right primary motor cortices (M1) both before and after the

motor learning task, in order to get maps of the GABA concentrations in M1 before and after motor learning (Fig. 1A, 1D).

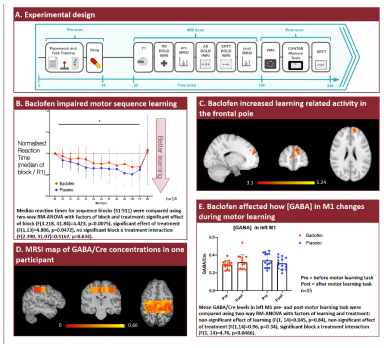
Behavioural data from the SRTT was analysed using two-way ANOVA with factors of learning and treatment. FMRI data was analysed using FMRIB Software Library (FSL; Jenkinson et al, 2012).

Results

Baclofen significantly impaired motor sequence learning ($p = 0.047$, Fig. 1B). These behavioural results were associated with changes in brain activation patterns during task performance: baclofen increased learning-related signal in the frontal lobe (Fig. 1C). While baclofen did not significantly change pre-task [GABA] in left M1 ($p > 0.05$), it did diminish the expected GABA decrease in M1 during motor learning ($p = 0.047$, Fig. 1E).

Conclusions

Our results showed that baclofen significantly impaired motor sequence learning and it also modulated the neural activity during motor learning and execution.



Prior expectations of motion direction modulate early sensory processing

Unique Code: TP001281

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Topic: Sensory and motor systems

INTRODUCTION

Perception is a process of inference, integrating sensory inputs with prior expectations. However, little is known regarding the temporal dynamics of this integration. It has been proposed that expectation plays a role early in the perceptual process, biasing sensory processing. Alternatively, others suggest that expectations are integrated only at later, postperceptual decision-making stages. The present study aimed to dissociate between these views.

METHODS

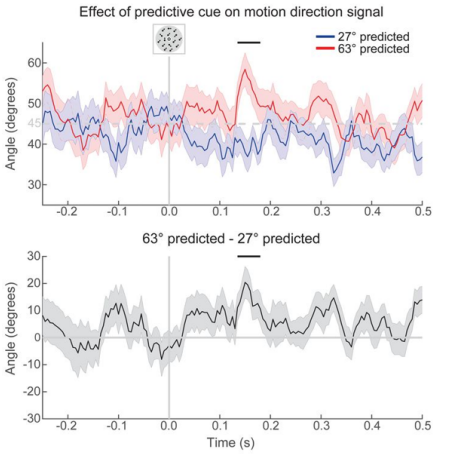
We exposed human participants (male and female, n=24) to auditory cues predicting the likely direction of upcoming noisy moving dot patterns, while recording neural activity using magnetoencephalography (MEG). After implicitly learning associations, participants' task was to report the predominant direction of moving dots.

STATISTICAL ANALYSIS

To investigate when expectations affected sensory representations, we used inverted encoding models, trained on independent localiser data, to decode the direction represented in early sensory signals. A linear subtraction of the mean decoded direction when one direction was predicted, from the decoded direction when the other direction was predicted, established when expectations modulated decoded direction. Between-subjects cluster-based permutation assessed whether neural modulation was related to subjective perception.

RESULTS AND CONCLUSIONS

Participants' reports of the moving dot directions were biased toward the direction predicted by the cues. Strikingly, the cues modulated the direction represented in the MEG signal as early as 150ms after visual stimulus onset. This reveals a modulation of early sensory representations. Exploratory analyses showed that the neural modulation was related to subjective perception: participants with a stronger perceptual bias toward the predicted direction also revealed a stronger reflection of the predicted direction in the MEG signal. For participants with this perceptual bias, a correlation between decoded and perceived direction already emerged before visual stimulus onset, suggesting that the prestimulus state of the visual cortex influences sensory processing. Together, these results suggest that expectations play an integral role in the neural computations underlying perception.



Expectation effects on decoded neural motion direction signals. Top: The mean decoded direction shown separately for the trials in which the direction 27° was predicted, and the trials in which 63° was predicted, in blue and red, respectively, as a function of time after the visual stimulus was shown. **Bottom:** The effects on decoding resulting from the predictive auditory cue, obtained as the linear subtraction of the decoded direction between these two cue conditions (i.e., 63° predicted; 27° predicted).

N-type calcium channels in pain pathway in vivo: PSNL increases CaV2.2 in deep layers of the dorsal horn

Unique Code: TP001299

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Topic: Sensory and motor systems

Introduction

Neuronal N-type (CaV2.2) voltage-gated calcium channels are important at the first synapse in the pain pathway. Here

we have used a knock-in mouse containing CaV2.2 with an extracellular HA-tag (1) to visualise, by inmunohistochemistry, the effect of sensory nerve injury on the distribution of N-type channels in dorsal root ganglion (DRG) neurons and their terminals following partial sciatic nerve ligation (PSNL). We hypothesise that the up-regulation of α2δ-1 associated with peripheral nerve injury (2) leads to an increase trafficking of CaV2.2 to primary afferent terminals that is impaired in the absence of α2δ-1.

Methods
We studied the expression of CaV2.2 in sections of lumbar spinal cord and DRGs of PSNL Cav2.2_HAKI/KI and double-transgenic Cav2.2_HAKI/KI; α2δ-1KO/KO mice. We also used markers of primary afferent terminals of the superficial dorsal horn (IB4, CGRP), or GFRα1 a member of the GDNF receptor family, expressed in Aß low threshold mechanoreceptors.

Confocal images acquired with Zeiss LSM710 were analysed with ImageJ (DRG) or Zen software (Spinal cord).

Statistical analysis
Data, analyzed with GraphPad Prism 9.0.2 will be shown as mean ± SEM. Statistical significance will be assessed by one-sample Wilcoxon test and Kruskal-Wallis (Dunn's post hoc test) for comparison between groups.

Results
Our preliminary results show an increase of N-type channels mainly in medium and large DRG neurons. In the spinal cord, as previously described (3), we found a loss of presynaptic terminals in superficial layers (I-II) of the ipsilateral dorsal horn, shown by a patchy deficit of IB4 and CGRP staining, which was accompanied by an overall loss of CaV2.2 of ~9% or 12%, with or without α2δ-1 respectively. We also found an increase in CaV2.2 of ~20 % in the medial deep dorsal-horn, but only in presence of α2δ-1, potentially corresponding to terminals of Aß low threshold mechanoreceptors, in areas of increased immunoreactivity to GFRα1, which has also been reported to increase following nerve injury (4).

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The role of crmp2 and stathmins in ocular motor system axon guidance

Unique Code: TP001311
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Topic: Sensory and motor systems

The ocular motor system (OMS) consists of three cranial nerves and six muscles. OMS nerves originate in the brainstem and extend their axons to their muscle targets near the eye. A precise sequence of axon guidance events is required for the development of the OMS and defects in this process can cause eye movement disorders in humans. The signalling protein alpha2-chimaerin (CHN1) plays a pivotal role in OMS development and G-o-F mutations in CHN1 can cause the

eye movement disorder Duane retraction syndrome (DRS). CHN1 is activated by extracellular signals and signals via a downstream cascade to the cytoskeleton to promote axon guidance. Our research has identified multiple putative binding partners to CHN1, including the cytoskeleton regulatory proteins CRMP2, STMN1 and STMN2 and the current research focuses on the potential roles of these proteins as downstream effectors of CHN1.

Interactions of CHN1 with CRMP2, STMN1 and STMN2 were visualised in cultured neurons using proximity ligation assay (PLA). The expression patterns of the proteins were assessed in zebrafish, using RNAscope in-situ hybridisation. chn1, as well as crmp2, stmn1 and stmn2 were knocked down in zebrafish using morpholino (MO) and the effects on OMS anatomy and function analysed using wholemount immunostaining and optokinetic reflex (OKR) respectively. chn1, crmp2, stmn1 and stmn2 MO injection was compared to standard MO using Fisher's exact test for anatomy and 2-way ANOVA for OKR. chn1 MO was combined with injection of a CRMP2, STMN1 or STMN2 mRNA.

PLA in cultured neurons confirmed interaction of CHN1 with the proteins of interest throughout the cell body and axon. In-situ hybridisation showed varying expression patterns of crmp2, stmn1 and stmn2 in the zebrafish oculomotor nucleus. Knockdown of the proteins resulted in defects to OMS anatomy and to horizontal eye movements. These phenotypes were similar to those seen following chn1 knockdown and in human DRS patients. Additionally, co-injection of CRMP2, STMN1 or STMN2 mRNA with chn1 MO was able, at least partially, to rescue the anatomical phenotype caused by chn1 knockdown. These results show that CRMP2, STMN1 and STMN2 all function downstream of CHN1 in OMS development and serve a vital role in the axon guidance of OMS neurons.

Using zebrafish as an in vivo model of the human eye movement disorder Duane's Retraction Syndrome

Unique Code: TP001312

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Topic: Sensory and motor systems

The ocular motor system (OMS) controls eye movement through the interaction of 3 cranial nerves and 6 extraocular muscles. The organisation of the OMS is well conserved across species, including in zebrafish. Duane's Retraction Syndrome (DRS) typically manifests in limited unilateral or bilateral abduction of the eye, where gaze is directed towards the ear, and results from miswiring of these cranial nerves. Studies have led to the identification of a number of autosomal dominant, missense mutations in CHN1, encoding the signalling protein α2-CHN. We have previously demonstrated a crucial role for α2-CHN in axon guidance within the OMS in integrating extracellular signals to direct cytoskeletal remodelling. However, the precise mechanism by which disease-causing mutations in CHN1 lead to DRS remains to be elucidated.

To further investigate the role of α2-CHN in DRS, we obtained two transgenic zebrafish lines harbouring gain-of-function (GOF) mutations in chn1, L20F and G228S. We established the Tg(chn1+/L20F) and Tg(chn1+/G228S) lines which were subsequently incrossed and obtained larvae in the expected Mendelian ratios. At 5 days post-fertilisation, we used a custom-built set-up to analyse the optokinetic reflex (OKR). Larvae were immobilised within a drum upon which a series of vertical stripes were projected. By varying parameters, such as velocity and contrast of the stripes, we assessed horizontal eye movement fitness.

The OKR assay was performed on at least 5 clutches of larvae for each transgenic line. These results were pooled and a

minimum of 18 individuals per genotype were analysed for statistical significance using one-way ANOVA followed by Tukey test. The OKR assay did not demonstrate statistically significant differences between genotypes for either transgenic line in eye range or saccadic velocity. However, both were decreased in Tg(chn1L20F/L20F) larvae, particularly for abduction. Gain, a measure of the ability of the eyes to track the stripes in response to varying parameters, again failed to reveal a statistically significant difference in fitness across Tg(chn1+/G228S) genotypes, but did indicate decreases in Tg(chn1L20F/L20F) larvae, particularly in adduction. These preliminary data indicate that the L20F mutation impaired horizontal eye movements in homozygous larvae. This model will be used to investigate the potential neuroanatomical defects causing these differences and to gain insights into the molecular mechanisms leading to DRS.

Identification of a source of presynaptic inhibition to non-peptidergic C-fibres

Unique Code: TP001333

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Topic: Sensory and motor systems

Inhibitory interneurons in the spinal dorsal horn play a crucial role in controlling transmission of somatosensory information to the brain. Spinal inhibition is diminished in some chronic pain states, and inhibitory interneurons therefore represent a potential target for therapeutic intervention.

Previous studies identified a population of inhibitory interneurons in lamina II that express the calcium binding protein calretinin (CR). The axons and dendritic trees of these cells are co-extensive with the plexus of non-peptidergic C-fibres (defined by expression of the Mas-related G protein-coupled receptor D; MrgD). MrgD afferents are thought to be mechano-nociceptors and their central terminals correspond to the central component of type I synaptic glomeruli.

We have found that lamina II cells expressing the RAR-related orphan receptor beta (RorB) in the RorB-CreERT2 mouse line comprise a subpopulation of inhibitory CR interneurons. This provides a means of identifying and manipulating the function of a subset of CR islet cells. We have used a combination of anatomical (confocal and electron microscopy) and electrophysiological techniques to characterise this population of interneurons and the synaptic connections within lamina II. We have used relevant statistical tests throughout, including two-way ANOVAs with Tukey multiple comparison tests. $P<0.05$ was considered significant.

Using a variety of genetic crosses, we have mapped the circuitry of RorB interneurons in lamina II. We have shown that the major excitatory input to these cells is from MrgD afferents and subsequently, the main output of the interneurons is back onto the MrgD central terminals. Electron microscopy confirms that these associations are inhibitory axoaxonic synapses, and therefore RorB interneurons are a source of presynaptic inhibition to type I glomeruli.

These results suggest that there is a significant synaptic association between non-peptidergic C-fibres marked by MrgD and a subpopulation of inhibitory CR islet cells. RorB cells are likely to play an important role in setting mechanical pain thresholds and are a potential therapeutic target.

Neural correlates of texture perception during active touch

Unique Code: TP001366

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Topic: Sensory and motor systems

Aims

One explores the environment through self-directed tactile interactions, termed active touch. However, the neural underpinnings of texture processing during active touch have yet to be examined. We investigated how different natural textures affect touch behaviour and cortical oscillatory changes.

Methods

Participants completed unilateral ~6s touch trials for silk, brushed cotton, and hessian textures. Electroencephalographic (EEG) data were collected with a 129-channel electrode net. EEG power during texture processing was evaluated using the event-related desynchronisation (ERD) method in alpha (8-12 Hz), beta (16-24 Hz), low gamma (30-48, 52-60 Hz), and high gamma (60-80 Hz) frequency bands. Novel force plate technology was utilised to compute individualised touch markers and total load exerted for each trial.

Approach for statistical analysis

Changes in ERD were assessed using classical analysis with epochs aligned to trial onset cues, and individualised touch analysis aligned to touch markers. Permutations and one-sampled t-tests were utilised to identify electrodes for further analysis. Repeated measures analyses of variance were used to test changes in ERD, subjective ratings, and total load (g) between textures.

Results and conclusions

Subjective ratings revealed silk as the most pleasant and smoothest, followed by brushed cotton, with hessian rated as the least pleasant and roughest. Total load did not differ significantly between textures. Oscillatory power changes associated with touch processing were observed over sensorimotor areas during tactile exploration. No significant differences in ERD between textures were found using epochs linked to trial onset. However, epochs defined using individualised, trial-specific touch markers showed a textural difference in ERD for alpha- and beta-band power over somatosensory regions, with bilateral increases in beta-band ERD for smoother textures and contralateral increases in alpha-band ERD for rougher textures.

Results suggest individualised EEG analysis of periods aligned to touch markers is more sensitive to cortical changes than classical analysis aligned to trial onset cues. Findings lay the groundwork for investigations of active touch in relation to oscillatory activity.

Outer hair cells as wide-band piezo-electric actuators in the inner ear

Unique Code: TP001377
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Topic: Sensory and motor systems

In the mammalian inner ear, outer hair cells (OHCs) are responsible for the detection of low-level sounds and the separation of different input frequencies. They do this by selectively amplifying the movement of the basilar membrane (BM) using a fast electromechanical property of OHCs, 'electromotility'. The molecular basis, at least in the apical cochlea, is a voltage-driven conformational change of a protein ('prestin'/SLC26A5) embedded in the OHC lateral surface. However, an unresolved problem is that the membrane low-pass filters the receptor potential generated by the OHC mechano-electrical transduction [1]. Precise biophysical studies of OHCs at the high frequency (basal) end of the cochlea have also been limited by patch clamp recording technology.

Here I consider the OHC as a mechanically loaded piezoelectric actuator [2]. The poster will describe a theoretical model using published data, but where statistical testing is not relevant. When an OHC is stretched, a rapid inward current can be measured whose voltage-dependence identifies prestin as the source [3]. The OHC length change is proportional to the prestin charge displacement, Q. It arises from the distortion of the cytoplasmic binding site for internal anions. With the correct mechanical phasing, the current, dQ/dt, can lead to cancellation of the effective cell capacitance and extend the OHC bandwidth. Such schemes can be incorporated into simple 2-D models of cochlear mechanics and lead to reduction of the viscous damping in the cochlear partition, allowing amplification.

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Pre-frontal cortical and lower limb muscle activity during walking in healthy older adults and Parkinson's disease; an integrated fNIRS and EMG study

Unique Code: TP001397
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Topic: Sensory and motor systems

Background: Gait decline in Parkinson's disease (PD) may be attributed to alterations in activity of the pre-frontal cortex (PFC) and lower limb muscles which are further exacerbated in dual-task (DT) walking. Complex neural networks integrate CNS and PNS information to coordinate locomotion. This study aims to investigate PFC and leg muscle activity that may reveal underlying mechanisms of gait control.

Methods: 15 healthy older adults (OA) (74 ± 6.9 yrs, m8, f7) and 30 people with idiopathic PD (71 ± 5 yrs, m19, f11) participated. PFC activity was recorded using functional near infra-red spectroscopy (Ocatamon, Artinis Med Systems). PFC oxygenated haemoglobin (HbO2) was determined using modified Beer-Lambert Law and normalised to single-task

(ST) walking. Wireless surface electromyography (EMG) measured: tibialis anterior (TA), medial gastrocnemius (MG), lateral gastrocnemius (LG) and soleus (SO). Participants walked overground for 300s (150s ST,150s DT). DT: recite total no. of odd/even numbers in audio during walking. EMG signal was band-pass filtered (7-395Hz) and intensity is reported after gait cycle segmentation, time and amplitude normalisation. Linear mixed effect models identified significant effects.

Results: TA and SO decreased ($p<0.01$) and LG increased ($p<0.01$) during DT relative to ST in OA and PD. PD exhibit greater reduction in TA during DT walking ($p<0.01$) compared to OA. PFC activation increases in OA but decreases in PD. Greater PFC associated with reduced MG and LG and DT score error in OA, but greater stance time in PD.

Conclusions: PFC and muscle activity alter during DT relative to ST walking. Reduced EMG intensity during DT of uniarticular muscles TA and SO and increase in biarticular muscle LG may relate to the different motion demands and inhibitory effects of LG on SO. Greater reduction in TA activity for PD may be associated with changes in sensorimotor impairment or foot placement that consequentially increases falls risk. Heightened PFC activation suggests greater executive resources are used to execute DT walking in OA. The opposite in PD may relate to pathology induced fronto-striatal dysfunction which deters elevated PFC activation. This may in turn alter muscle activity that ultimately disrupts efficient gait control.

Synapses and plasticity

Understanding the effect of tubulin post-translational modifications on axonal transport in C. elegans

Unique Code: TP001029
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Topic: Synapses and plasticity

A remarkable number of post-translational modifications (PTMs) on tubulin and microtubules (MTs) have been identified that affect MT dynamic, stability, organization and its interaction with motor proteins (such as kinesin and dynein) in neurons. Dysfunctional axonal transport has a large impact on synaptic transmission affecting memory and synaptic plasticity often leading to neurological disorders. I investigate the role of three different PTMs glutamylation, tyrosination, and acetylation on axonal transport of UNC-104 (kinesing-3/KIF1A) and its cargo RAB-3 in C. elegans, used motor motility assays, in situ immunostaining, co-immunoprecipitation assays and in vivo protein-interaction assays (BiFC) etc.

For statistical analysis, I used one-way ANOVA and t-test to analyze the results. In polyglutamulase mutants (TTLL-11) worm's velocities and run lengths of both UNC-104 and its cargo RAB-3 were significantly reduced as compared to wildtype. Further, tubulin polyglutamylation in worm lysates after TTLL-11 knockout consistent with reduced fluorescence in whole mount staining using Poly E GT335(sigma) antibodies. On the other hand, knocking out deglutamylase CCPP-1 does neither affect motility for both motor and its cargo. Interestingly, UNC-104 interacts with glutamylase enzymes in ccpp-1 mutant worm lysates when employing in co-IP assays. Additionally, in worms carrying a mutation in tyrosine ligase TTLL-12, kinesin-3 UNC-104 and its cargo RAB-3 exhibit reduced motility and increased pausing times compared to wildtype. Similarly, in acetylation mutant worm's mec-17 the velocity and run lengths of both UNC-104 and its cargo RAB-3 were also significantly reduced consistent with observations on kinesin-1 by others.

We hypothesize that these changes in axonal transport efficiencies are related to differentially post-translational modified tubulins. We believe that our basic research will provide important mechanistic insights important for drug design to prevent or cure neuronal diseases such as tubulinopathies.

The neuroprotective effects of leptin in a model of tau-related synaptic dysfunction

Unique Code: TP001031

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Topic: Synapses and plasticity

Accumulation of amyloid-beta and hyperphosphorylated tau into plaques and neurofibrillary tangles are hallmarks of Alzheimer's disease (AD). Soluble oligomers of amyloid-beta and tau can promote synaptic dysfunction, and synaptic deficits within the hippocampus are thought to underlie the memory deficits observed in early AD. Recently, aberrant leptin production and signalling has been reported in AD patients, indicating that leptin has neuroprotective properties within the hippocampus. Accumulating evidence has shown leptin to be protective against the toxic effects of amyloid-beta, including its ability to prevent amyloid-beta-induced cell death and inhibition of long-term potentiation at hippocampal synapses. However, the effects of leptin on tau-related synaptic dysfunction are unclear. Using immunocytochemistry, we show that amyloid-beta application to primary hippocampal neurons induces migration of tau from axons to dendrites and synapses, with amyloid-beta treatment (1micromolar, 1hr) resulting in a 75% increase in dendritic tau compared to control ($p<0.001$, n=48 dendrites). Amyloid-beta application also increases expression of phosphorylated tau (p-tau) at synapses as indicated by increased % colocalization of p-tau and PSD-95 from 43% to 57% ($p<0.001$, n=36 dendrites). Treatment with leptin can prevent this aberrant targeting of tau to dendrites and synapses as dendritic tau levels and % colocalization are not significantly different from control in leptin plus amyloid-beta treated neurons ($p>0.05$, n=48 dendrites). Thus, these data suggest that leptin possesses neuroprotective properties in our model of tau-related synaptic dysfunction. These findings expand on previous research investigating the protective actions of leptin and further validates leptin as a therapeutic target in Alzheimer's disease.

Dissecting function and the molecular pathways of SFXN-1.2 in mitochondrial dynamics and its effects on worm behavior and neurodegeneration

Unique Code: TP001032

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Topic: Synapses and plasticity

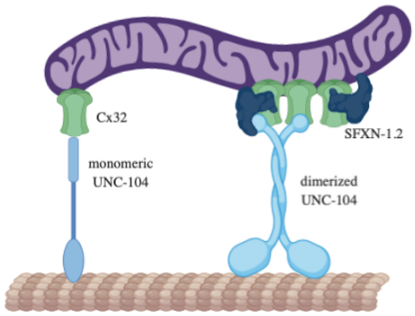
Mislocalizations of mitochondria and alterations in mitochondrial dynamics are the hallmarks in various neurological diseases. Thus, it is critical to understand how the dynamics of mitochondria are regulated on the molecular level. From a candidate screen (95 genes), we have identified a novel gene called sfxn-1.2 (ortholog of human Sideroflexin 1/3), a mitochondrial protein enriched in neurons associated with Alzheimer's disease and Parkinson's disease. Since the function of sfxn-1.2 in mitochondrial transport at the molecular level is unknown, we aim to dissect the function and the molecular pathways of SFXN-1.2 in mitochondrial dynamics and its effects on worm behavior and neurodegeneration.

The methods used are, (1) worm culture and microinjection of the cloned plasmid into gonads of the worm, (2) imaging of worms, (3) motility analysis (4) Oroboros O2k-FluoRespirometer to measure oxygen consumption (5) RNAi knockdown using the feeding method, (6) CRISPR/Cas9 gene editing to generate knockouts, (7) Co-IP assays (8) Real-time PCR assays

(9) Touch assays to detect mechanosensory defects, (10) Paralysis assay to detect defects in acetylcholine neurotransmission.

For Statistical analysis, to compare two groups, we use unpaired, two-tailed Student's T-test. For more than two groups we use One-Way ANOVA with Dunnett's test for multiple comparisons to the control group.

We observed that SFXN-1.2 is associated with significant changes in mitochondrial morphology and trafficking in neurons. Our results suggest a possible direct interaction between UNC-104 and mitochondria. The role of UNC-104 (KIF1A) in mitochondrial transport will have a strong impact because since decades it is thought that KIF5 and KIF1Bα are the only transporters of mitochondria. Our data reveal possible motor neuron defects and sensory neuron defects in sfxn-1.2 mutants. Thus, these investigations will aid to develop novel drugs to target neurological diseases based on defects in mitochondrial transport.



Visualisation of the native N-type calcium channel at presynaptic terminals

Unique Code: TP001085

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Topic: Synapses and plasticity

N-type calcium channels (CaV2.2) are important for neurotransmitter release in the central and peripheral nervous system. Immunohistochemical detection of native CaV2.2 has not yet been possible until now due to its low expression and lack of antibodies to surface accessible epitopes of the channel. The present study utilises the recently developed constitutive knock-in (KI) transgenic mouse, expressing CaV2.2 with an epitope tag (2 x haemagglutinin; HA) inserted in the extracellular loop between S3 and S4 of domain II (CaV2.2_HAKIKI). The tag does not affect the function of the channel when expressed in vitro (Cassidy et al., 2014). In the somatosensory nervous system, CaV2.2_HA is expressed on the cell surface of dorsal root ganglion (DRG) neurons and in the primary afferents terminating in the dorsal horn of the spinal cord (Nieto-Rostro et al. 2018). The present study uses the CaV2.2_HAKIKI mouse to exclusively study the presynaptic expression of N-type calcium channels in presynaptic terminals of co-cultures between DRG and spinal cord neurons. Super-resolution images of the presynaptic terminals reveal an increase in CaV2.2_HA expression over time in culture. Conversely, at the DRG cell bodies, a significant down-regulation of cell surface CaV2.2_HA expression is observed throughout the development of these co-cultures (one-way ANOVA). Similarly, CaV2.2 mRNA expression in DRG tissue shows a marked decrease over development (Student's t-test). These co-cultures will be instrumental in future studies to enhance our understanding of the presynaptic role of endogenous N-type calcium channels in physiological and pathological states.

Nieto-Rostro, M., Ramgoolam, K., Pratt, W. S., Kulik, A. and Dolphin, A. C. (2018), 'Ablation of α2δ-1 inhibits cell-surface trafficking of endogenous N-type calcium channels in the pain pathway in vivo', Proceedings of the National Academy of Sciences115(51), E12043–E12052.

Visualising Tripartite Synapse Nanostructural Changes in Amyotrophic Lateral Sclerosis

Unique Code: TP001089

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Topic: Synapses and plasticity

Synapses are the communication junctions between neurons in the nervous system. They consist of thousands of proteins organised into trans-synaptic signalling clusters (nanoclusters, 'NCs') that facilitate high fidelity signal transmission. Astrocytes make specialised contacts with synapses, termed tripartite synapses, where they are capable of detecting and manipulating synaptic activity. Both synapses and astrocytes are thought to show altered functionality in pathological conditions such as Amyotrophic Lateral Sclerosis (ALS). This study aims to investigate synaptic and tripartite synaptic nanostructure in the spinal cord in ALS mice. To visualise tripartite synapses, mice expressing PSD95-eGFP were used to visualise the excitatory postsynaptic density (PSD), along with immunolabelling of other synaptic and astrocytic structures. PSD95-eGFP mice were crossed with G93a-SOD1 mice, WTSOD1 mice and C9orf72 mutant mice (C9BAC). Approximately 10 million synapses and tripartite synapses have been visualised and analysed using high-resolution and super-resolution microscopy (g-STED) to produce a robust map of tripartite synaptic changes in ALS. Large-scale high-resolution inter-laminae data sets and control-versus-disease comparisons of synapse parameters, were analysed using Two-Way ANOVAs from averaged data values per mouse. A range of other parametric and non-parametric statistical analyses were performed depending on the specific data sets. In the healthy adult mouse spinal cord, there is anatomical diversity in PSD nanostructure whereby ventral horn synapses are larger with a greater number of PSD95 NCs. We find that early-symptomatic 16-week-old G93a-SOD1 mouse spinal cords display widespread changes in PSD density and nanostructure, notably in the lateral motor pools. No such synaptic changes were observed in WTSOD1 mice or in C9BAC mutant mice, neither of which display ALS motor phenotypes. Tripartite synapses, as determined by their association with presynaptic VGLUT2 and astrocytic EAAT2 or pEzrin, show a greater nanostructural complexity and enriched expression of PSD95. In symptomatic G93a-SOD1 mice, the fraction of synapses which are tripartite are reduced compared to controls. These findings demonstrate that tripartite synapse nanostructure is altered ALS, which may lead to changes in neuronal excitability which could correspond to motor deficits. Fundamentally, this work also demonstrates the importance of nanoscale analysis of synaptic and astrocytic structure for understanding neural function in health and disease.

Tonic inhibition of mesostriatal dopamine release by striatal A1 adenosine receptors and regulation by astrocytic equilibrative nucleoside transporter

Unique Code: TP001092

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Topic: Synapses and plasticity

1. Introduction

Striatal dopamine (DA) is critical for action and learning, and DA release is gated by mechanisms operating directly on striatal axons. Adenosine (Ado) plays important roles in modulating neurotransmission across the CNS and in striatum is thought to inhibit DA output via action at A1 receptors. An extracellular Ado tone is reported in striatum that is limited by equilibrative nucleoside transporters (ENTs) primarily located on striatal astrocytes, but whether striatal DA release is under tonic inhibition by an Ado tone and, by extension, is regulated by striatal ENTs is unknown.

2. Methods

Here we investigated whether striatal Ado can modulate DA output using fast-scan cyclic voltammetry at carbon fibre microelectrodes to detect DA release in real-time in acute slices of mouse striatum, in combination with Ado detection using a GPCR-activation-based Ado sensor (GRABAdo) and Ado pharmacology.

3. Approach for statistical analysis

For all experiments, data were collected from a minimum of four animals and data were compared for statistical significance using a two-way repeated-measures ANOVA. Both male and female mice were used in this study.

4. Results and conclusions

We reveal that endogenous striatal Ado signalling can powerfully modulate DA output through action at A1Rs. DA release evoked by single electrical pulses was inhibited by Ado or A1R agonists, but not A2AR agonists, with effects prevented by selective A1R antagonists. A1R agonists also suppressed DA release evoked by optogenetic stimulation of DA axons. A1R activation was found to significantly enhance the frequency- and activity-sensitivity of DA release, suggesting that A1Rs change the gain on DA release. Antagonists of A1Rs significantly enhanced DA release evoked by either single optogenetic or electrical stimuli, indicating that there is an A1R-mediated tonic inhibition of DA release by a striatal Ado source. Inhibitors of ENT1 were found to attenuate evoked DA release through increasing tonic A1R-mediated inhibition of DA release via enhanced striatal Ado tone measured using a GRABAdo sensor. These data define previously unappreciated roles for A1Rs, and by extension Ado tone and ENT1, in determining striatal DA release, and corroborate emerging data highlighting astrocytic transporters as important regulators of striatal function.

Glycine reduces evoked striatal dopamine release in a region-dependent manner

Unique Code: TP001126

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Topic: Synapses and plasticity

Introduction
Despite evidence of striatal glycinergic transmission, its potential modulation of dopamine (DA) transmission is poorly understood. Microdialysis studies have shown that GlyR ligands alter extracellular DA concentrations ([DA]o) but with conflicting outcomes. We explored if GlyR ligands alter evoked DA and acetylcholine (ACh) release in striatum, monitored in real-time using electrochemical and fluorescent sensors.

Objectives
Identify whether glycine alters evoked DA release in mouse striatum, differentially between dorsolateral caudate putamen (dlCPu) and nucleus accumbens core (NAc), via glycine receptors (GlyRs) or other receptors. Address whether glycine transporter 1 (GlyT1) modulate this action.

Methods
Experiments were conducted in acute brain slices of C57Bl6/J mice striatum. Extracellular DA concentration ([DA]o) was detected using fast-scan cyclic voltammetry at carbon-fibre microelectrodes1. ACh was detected with the GRABACh3.0 sensor2. Local bipolar electrical stimulation evoked transmitter release. Ligands glycine (1-10 mM), taurine (10 mM), strychnine (10 µM), sarcosine (500 µM), DHβE (1 µM), bicuculline (10 µM), CGP-55845 (4 µM), AP-V (50 µM) were bath-applied.

Statistical analysis
Experiments involved at least 3 animals, males and females. Effect of GlyR agonists used internal controls, and repeated-measures design. Comparison of glycine effect between regions and under antagonist conditions used time-matched controls. Parametric statistical tests used.

Results
Applied glycine reduced evoked [DA]o in the striatum, to a greater extent in dlCPu than NAc. In dlCPu, GlyT1 inhibition enhanced the effect of glycine, but alone did not alter evoked [DA]o. GlyR agonist taurine and, paradoxically, GlyR antagonist strychnine both reduced evoked [DA]o. Glycine increased the frequency-dependence of DA release, which was occluded by nAChR antagonism. Glycinergic modulation of ACh release will be reported. GlyR modulation of evoked [DA]o was not mediated via actions on other circuits involving NMDA-Rs or GABA-Rs.

Conclusion
Glycine reduces DA release in dorsal more than ventral striatum, via a partially nAChR-mediated mechanism.

1. Threlfell et al.,Neuron;75:58-64(2012)
2. Jing et al.,Nature Methods;17:1139-1146(2020)

Striatal dopamine transporter function is facilitated by converging biology of ?-synuclein and cholesterol

Unique Code: TP001143

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Topic: Synapses and plasticity

Objectives

To test whether dopamine transporter (DAT) function in governing dopamine (DA) uptake and release is modified in a transgenic mouse model of early Parkinson's disease (PD). To explore converging biology of α-synuclein and cholesterol and how they impact on DAT function to provide insights into the aetiology and progression of PD.

Introduction

Striatal DATs regulate DA signalling, and can contribute risk to degeneration in PD. DATs can interact with α-synuclein, which is associated with the aetiology and molecular pathology of idiopathic and familial PD. DAT function is highly regulated and interacts with peptides and lipid partners including α-synuclein and cholesterol. Cholesterol and α-synuclein also interact.

Methods

Using fast-scan cyclic voltammetry (FCV) to detect DA release in ex vivo acute striatal slices from a human-α-synuclein-overexpressing (SNCA-OVX) transgenic mouse model of early PD and α-synuclein-null controls, and biochemical assays: quantified Western blot, immunohistochemistry, proximal ligation assay and radioligand-binding assay. Cholesterol levels measured with ToF-SIMS.

Statistical analysis

Parametric tests were used when data were normally distributed (Shaprio-Wilk) with equal variances. For multiple comparison tests one- or two-way ANOVAs with Dunnett's or Sidak's posttests. Data are mean ± SEM with individual data points illustrated.

Results

SNCA-OVX mice had elevated DA uptake rates, and more pronounced effects of DAT inhibitors and on short-term plasticity (STP) in DA release. We found that DAT membrane levels and ligand-binding correlated with α-synuclein level. Furthermore, DAT function in snca¬-null and SNCA-OVX mice were also be promoted by applying cholesterol. Using Tof-SIMS we found genotype-differences in striatal lipids, with lower striatal cholesterol in SNCA-OVX mice. An inhibitor of cholesterol efflux transporter ABCA1 or a cholesterol chelator in SNCA-OVX mice reduced the effects of DAT-inhibitors on evoked [DA]o.

Conclusions
These data indicate that human α-synuclein promotes striatal DAT function, in a manner supported by extracellular cholesterol, suggesting converging biology of α-synuclein and cholesterol that regulates DAT function.

Genetic Mutations Underlying Congenital Stationary Night Blindness: Loss of Phototransduction and Synaptogenesis

Unique Code: TP001184
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Topic: Synapses and plasticity

Introduction:
Development of the eye relies on complex and coordinated driving forces throughout the embryonic period. Any disruption to this initial patterning and differentiation of specialised cells may culminate as a congenital abnormality. Congenital stationary night blindness (CSNB) is both a clinically and genetically heterogeneous inherited retinal disease that arises as a result of mutations in one of several genes. This paper aims to comprehensively analyse mutations of the genes implicated in CSNB and with respect to CACNA1F, identify the anatomical implications these mutations have.

Methods:
A literature search of the database PubMed was performed from inception to present and the references of all included studies were searched for relevant literature. 997 articles were initially identified with 81 articles being included in the review, after both the inclusion and exclusion criteria were applied.

Approach for statistical analysis:
No statistical analysis was undertaken.

Results and conclusions:
Results have shown that mutations in the genes involved in the phototransduction cascade (GNAT1, RHO and PDE6B) cause autosomal dominant CSNB, whilst those arising downstream from this cascade present as complete (GRM6 and NYX) and incomplete (CACNA1F, CABP4 and CACNA2D4) CSNB. Mutations in CACNA1F, which encodes the alpha 1-subunit of the Cav1.4 channel, lead to X-linked CSNB. In addition to functional changes in this channels ability to conduct calcium and thus 'propagate' electrical signals, disruption of synaptogenesis between the photoreceptor and bipolar cell synapses is likely to occur as a result of these mutations, offering a potential target for future therapeutic options, which could aim to treat synaptopathic abnormalities.

Opposing polarity and temporal properties of NTS POMC neuron opioidergic and glutamatergic neurotransmission with DMV cells in the medulla

Unique Code: TP001267
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Topic: Synapses and plasticity

Proopiomelanocortin (POMC) expressing neurons in the nucleus of the solitary tract (NTS) have profound control over cardiorespiratory function. Their sub-second actions on heart rate are likely mediated by excitatory neurotransmission, whilst also being opioid dependent (1). Here we investigate the mechanism of NTS POMC neuron opioidergic transmission with their postsynaptic targets within the medulla oblongata, focusing on nuclei involved in vago-vagal reflexes.

Whole cell patch clamp recordings from dorsal motor nucleus of vagus (DMV) neurons, a region shown to innervate the heart, were conducted in acute medulla slices. POMC-Cre mice (2) received stereotaxic injection of a Cre-dependent adeno-associated virus to modulate NTS POMC neuron activity. Optogenetic activation (AAV2-EF1α-DIO-ChR2(H134R)-mCherry) was used to evoke synaptic release from POMC neurons and chemogenetic silencing (AAV2-hSyn-DIO-hM4D(Gi)-mCherry) allowed investigation of tonic spontaneous synaptic release on target nuclei.

NTS POMC neurons are spontaneously active (4.5±1.7 Hz, n=9) and are thought to provide a tonic opioid inhibitory tone on their postsynaptic target cells in the DMV limiting action potential frequency (control 2.1±1.2 Hz, CTAP 4.3±1.2 Hz, p=0.03, Wilcoxon signed ranks test, n=6/13). This tone is μ-opioid receptor dependent, as it is absent in knock out mice (control 4.5±1.4 Hz, CTAP 3.5±1.0 Hz, paired sample t-test, n=7/7).

POMC neuron inhibition primarily reduces DMV cell firing (control 3.9±0.8 Hz, CNO-dihydrochloride 3.0±0.7 Hz, p=0.05, paired sample t-test, n=11). Sub-second optogenetic activation of POMC neurons evokes glutamatergic EPSCs in the DMV. We postulate that the DMV cells showing reduced firing upon POMC neuron silencing, are cells not receiving β-endorphin, so the outcome is reduced glutamatergic input. The occasional excitatory response to POMC neuron silencing fits with a loss of tonic β-endorphin presynaptic negative modulation of glutamate release.

The opposing polarity and temporal properties of the two modes of POMC neuron transmission with DMV cells, provides support for similar control at major cardiorespiratory nuclei within the medulla.

(1) Cerritelli S et al (2016). PLoS One 11(4)
(2) Balthasar N et al (2004). Neuron 42(6)

Common synaptic transmission arising from diverse mutations in the human NMDA receptor subunit GluN2A

Unique Code: TP001276

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Topic: Synapses and plasticity

Dominant mutations in the human gene GRIN2A, encoding NMDA receptor (NMDAR) subunit GluN2A, make a significant and growing contribution to the catalogue of published single-gene epilepsies. Understanding the disease mechanism in these epilepsy patients is complicated by the surprising diversity of effects that the mutations have on NMDA receptors as assessed in heterologous expression systems. As a step to understanding genotype-phenotype correlation, we measured the effects that severe gain- and loss-of-function GRIN2A mutations have on excitatory synaptic transmission.

To select mutations for this study, we used exploratory factor analysis and k-means clustering on functional data published for 20 NMDA receptor mutations. We were able to identify 2 mutations with overall severe gain-of-function (GOF: L812M, K669N) and 3 mutations with severe loss-of-function (LOF: C436R, T531M, R518H). The mutants were cloned using the human cDNA for GRIN2A, which was cotransfected with Cre-GFP into CA1 neurons within organotypic hippocampal slices prepared from Grin2afl/flbfl/fl or Grin2afl/fl mice. Electrical stimulation of the Schaffer collateral axons was combined with recording of the synaptic currents simultaneously in transfected and untransfected neurons. Data were analysed by Bayesian multivariate multilevel modelling using a weakly informative prior.

Consistent with their classification, GOF (but not LOF mutations) were effective at rescuing NMDAR-EPSCs in CA1 cells from Grin2afl/flbfl/fl slices and these currents exhibited slower deactivation compared to WT. Surprisingly though, molecular replacement experiments in Grin2afl/fl mice produced similar NMDAR-EPSC current decays across all mutations, ranging from 1.4 to 2-fold slower than for wildtype receptors. The peak amplitudes of mutant-associated NMDAR-EPSCs were also smaller than WT, leading to no overall net change in charge transfer. Modelling in the NEURON simulation environment was used to explore the impact that these changes in NMDA receptor conductances would have on depolarizations during bursts of high-frequency synaptic activity.

Postsynaptic structural organisation in sign- and goal- tracking rats

Unique Code: TP001277

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Topic: Synapses and plasticity

Introduction

Cues associated with rewards can acquire incentive properties and gain control over behaviour, potentially leading to maladaptive behaviours. In studies using rats, animals that are attracted to reward-paired cues and attribute them with motivational value are called sign-trackers (STs). In contrast, goal-trackers (GTs) assign predictive value to reward-cues and are not attracted to them. Much research has focused on presynaptic mechanisms underlying this individual variation. Here, we assessed whether sign- or goal-tracking is associated with unique postsynaptic organisation (e.g., dendritic spine density and properties) in the nucleus accumbens (NAc).

Methods

Lister Hooded male and female rats were trained using a Pavlovian conditioned approach procedure to identify sign- and goal-trackers (5-days of pairing a lever-cue with food reward). A separate ‘no-learning’ control group was tested, for which lever presentation did not predict reward. During a final session, all rats were re-exposed to the lever. After 30min or 6h, brains were removed and prepared for neuroanatomical analysis (Golgi-impregnation). Stained dendrites in the NAc core were reconstructed using Neurolucida and dendritic properties were analysed.

Statistical approach

Data distribution was first assessed to confirm the use of parametric tests. Behavioural data was analysed using t-tests

and repeated-measures ANOVAs with post-hoc tests. Dendritic morphology was analysed with linear regression and two-way ANOVAs with post-hoc tests.

Results
Conditioned rats of both sexes were predominantly categorised as STs (n=45; 77.8%). As expected, the no-learning control group (n=11) did not develop conditioned behaviour. We did not observe any effect of the re-exposure to the cue, nor any sex differences, on spine properties in STs and GTs. Control rats tended to display a higher density of spines than conditioned rats, but analyses are ongoing.

Conclusion
The discrete reward cue does not appear to induce postsynaptic structural changes in the NAc core, which suggests that other brain areas might be more relevant for this mechanism. These data offer the possibility of further understanding incentive motivational neural processes, including how they relate to gender differences.

Detecting Silent Synapses with Live-cell Imaging

Unique Code: TP001291
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Topic: Synapses and plasticity

Silent synapses are widely described as synapses that express N-methyl-D-aspartate receptors (NMDARs) but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs). These synapses have extremely low synaptic efficacy at resting membrane potentials. Silent synapses became an area of great interest since their unsilencing presents a novel mechanism for synaptic plasticity and their dysregulation is associated with neurodevelopmental disorders. To date, the identification of silent synapses has been achieved using electrophysiology or immunocytochemistry. However, the lack of real-time readout from immunocytochemical experiments and the indirect nature of electrophysiological recordings that lack information on synapse location, limits our ability to measure the distribution and usage of silent and active synapses. We propose a novel live-cell optical imaging approach for detecting silent synapses, which could further our understanding of their dynamics and distribution. Using computational modelling in combination with imaging experiments, we have optimised recording conditions to distinguish silent form active synapses and map-out silent synapses in cultured hippocampal neurons. Spinning disk confocal imaging of presynaptic glutamate release using SF-iGluSnFR.A184S (iGluSnFR) was performed simultaneously with detection of postsynaptic, depolarisation-dependent activation of NMDARs using the Ca2+ indicator CalBryte-590 (CalBryte). In the absence of extracellular Mg2+ and action potential firing, spontaneous miniature postsynaptic Ca2+ transients were reliably detected, with the majority of iGluSnFR events resulting in coincident postsynaptic Ca2+ transients. The Ca2+ transients were reliably abolished with an NMDAR antagonist, confirming the source of the Ca2+. The capacity of this tool to discriminate between active and silent synapses was validated through the application of AMPAR blockers (NBQX and GYKI-52,466), which resulted in a total absence of postsynaptic Ca2+ signal despite the presence of an iGluSnFR signal. Interestingly, under conditions of zero magnesium, the residual population of iGluSnFR events without resulting postsynaptic Ca2+ transients suggests that a fraction of synapses do not express functional NMDARs.

Visualizing presynaptic short-term plasticity at individual boutons

Unique Code: TP001303

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Topic: Synapses and plasticity

An action potential arriving at a presynaptic terminal opens voltage-gated calcium channels, causing an influx of calcium that drives neurotransmitter release. Synapses are heterogeneous in release probability and in turn, the dynamics of neurotransmitter release during trains of action potentials (short-term plasticity). Whilst some synapses respond by initially releasing weakly and gradually increasing release during a burst (facilitation), others do so by releasing strongly to begin with and gradually ramping down (depression). What underlies this functional diversity is not fully understood, although several mechanisms have been proposed including differences in the number of release sites or the coupling distance between calcium channels and release sites, expression of specific calcium sensors such as Syt7 for facilitation, and short-term modulation of specific calcium channel subtypes.

To visualize calcium entry and vesicle exocytosis simultaneously in individual synapses, we constructed sypHy-RGECO, a fusion of the synaptic vesicle protein synaptophysin with a GFP-based pHluorin sensor and the red calcium indicator RGECO (Jackson and Burrone 2016). Using phorbol esters we confirmed that we can monitor independent changes in the two processes, increasing vesicle release without increasing calcium influx. By comparing responses to single, paired or bursts of action potentials in dissociated hippocampal neurons, we identify individual synapses displaying either depression or facilitation of neurotransmitter release. We also observe short-term changes in calcium influx that exhibit a complex relationship with release dynamics.

In agreement with previous studies we find that increasing external calcium concentration increases release probability and calcium influx, whilst decreasing facilitation. Similarly, we observe greater short-term plasticity with shorter interstimulus intervals and a decrease in facilitation in Syt7 knockout neurons. Our ongoing work involves using calcium chelators to investigate the channel-vesicle coupling distance at individual synapses and exploring the involvement of different subtypes of calcium channels in the plasticity of both release and calcium dynamics.

Jackson and Burrone 2016. Front Synaptic Neurosci. 8:21

Subcellular sorting of neuregulins controls the assembly of cortical circuits

Unique Code: TP001330

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Topic: Synapses and plasticity

The cerebral cortex harbours an intricate network of interconnected cell types that is essential for sensory perception and cognitive function. The assembly of neuronal circuits requires the expression of complementary molecular programs in pre and postsynaptic neurons. The signalling pathway mediated by members of the neuregulin (Nrg) family of trophic factors and their kinase receptor ErbB4 plays a fundamental role in circuit development and synapse formation. Yet, the precise function of neuregulin proteins in the wiring of cortical circuits during postnatal development remains unclear.

We generated inducible conditional knockout mice to delete Nrg1 and Nrg3 specifically in pyramidal cells during postnatal development. Imaging analysis were used to assess the effect on synaptic connectivity in the cerebral cortex. Gain-of-function experiments were performed via in utero electroporation. To explore mechanisms underlying neuregulin specificity, we generated a battery of chimeric constructs to examine their effects in cortical connectivity in vivo.

Quantifications were conducted in more than three mice from three separate litters for each experimental condition. For synaptic density analysis, more than 20 individually reconstructed neurons were analysed per animal. For subcellular distributions, more than 30 independent regions of interests were analysed per animal. Statistical methods included t-test, Mann-Whitney U-test, one-way ANOVA, and post-hoc Tukey's range test.

We found that Nrg1 and Nrg3 exhibit selective functions in cortical circuit assembly by differentially regulating the formation of inhibitory and excitatory synapses, respectively. The specific role of Nrg1 and Nrg3 in this process is not due to their receptor-binding EGF-like domain, but rather to their distinctive subcellular localisation within pyramidal cells. Our experiments uncover how the control of subcellular localisation underlies the function of the neuregulin/ErbB4 signalling pathway in specific synaptic connections. This study reveals a novel strategy for the assembly of cortical circuits during postnatal development that involves the differential subcellular sorting of family-related synaptic proteins.

Reducing voltage dependent potassium channel 3.4 levels ameliorates synapse loss in a mouse model of Alzheimer's disease

Unique Code: TP001371

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Topic: Synapses and plasticity

Synapse loss is the strongest pathological correlate of cognitive decline in Alzheimer's disease, which likely contributes to the devastating cognitive decline experienced by patients. Owing to their plastic nature, synapses are an ideal target for therapeutic interventions that offer potential for restoration following treatment. KV3.4 is a voltage-gated potassium (K+) channel known to play an important role in controlling neuronal firing and aspects of synaptic plasticity in the brain. Previous work has shown KV3.4 channels are upregulated in post-mortem brain tissue from people who died with Alzheimer's disease and in mouse models of amyloidopathy. Here we tested the hypothesis that plaque-associated synapse degeneration could be rescued in a mouse model expressing human amyloid precursor protein (APP) and presenilin 1 (PS1) carrying mutations that cause familial Alzheimer's disease. In these APP/PS1 mice and wild-type littermates, we injected a virus to knock down KV3.4 using CRISPR/Cas technology and a fluorophore to label neurons (enhanced yellow fluorescent protein) in one hemisphere and a control virus to label neurons (tdTomato) in the contralateral hemisphere. Linear mixed effects models were used to analyse data with mouse as a random effect to

account for multiple measurements per mouse. Genotype, treatment (KV3.4 knockdown or control), sex, and plaque proximity (in APP/PS1 mice only) were fixed effects. Assumptions of the model fit were tested by visual inspection of residual plots. In the case of KV3.4 staining intensity, the data were Tukey transformed to better fit model assumptions. Analysis of variance tests were run on linear mixed effects models to examine main effects and estimated marginal means with Tukey corrections were used for post-hoc group comparisons. We observed a knockdown of KV3.4 levels of approximately 20% in neurons expressing the CRISPR/Cas virus. Lowering KV3.4 levels was associated with increased dendritic spine density in both wild-type and APP/PS1 mice. In APP/PS1 mice, dendritic spine density was restored to control levels. These results suggest that KV3.4 downregulation could be protective against Aβ-induced synaptic alterations.

Neuromorphology in ASC: The Eker Rat Model

Unique Code: TP001395

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Topic: Synapses and plasticity

Autism Spectrum Conditions (ASC) are a group of neurodevelopmental disorders with male bias characterised by deficits in social communication and interaction as well as displaying restricted repetitive behaviours. ASC are considered to be complex genetic disorders with 80% heritability, many of the implicated genes being involved in dendritic spine pruning and development via the mammalian target of rapamycin (mTOR) signalling pathway. Tuberculosis genes 1 and 2 (Tsc1 and Tsc2) directly work to inhibit mTOR activation. Human mutation of either gene leads to the genetic disorder, Tuberous Sclerosis Complex (TSC), which has a 50% comorbidity with ASC. Tsc haploinsufficiency in rats (Eker model) leads to social behaviour deficits which may be representative of the human ASC phenotype. Human postmortem studies have shown increased spine density in ASC patients compared to controls. However, both human and animal models of ASC have shown inconsistent results for spine morphology, which may underlie functional connectivity. To date, this has not been investigated in the Eker model. Therefore, we investigated sexual dimorphism in spine density/morphology in a nucleus shown to be important in ASC, the Medial Amygdala (MeA).

Dendritic spines were analysed in MeA stellate branchy neurons in Tsc 1+/- and wild-type (WT) male and female rats. Neuron images were captured using a light microscope and analysed using the FIJI (NIH Image) software. Student's T-test was used for hypothesis testing between control and test group means. Results shown as group means and error calculated as standard error of the mean. All statistics were performed using Prism (Graphpad, CA).

Increased spine density was found in male Eker rats compared to controls whereas no difference was found within females. Spine morphology analyses found increased mature spine morphology within male Ekers compared to controls. Females were also found to have increased mature spine morphology, however this was accompanied by a seemingly compensatory increase in immature type spines. These morphological differences may reflect the lack of behavioural deficits found within female ASC models compared to males. This study is the first to explore sex differences in spine density and morphology in any ASC model.

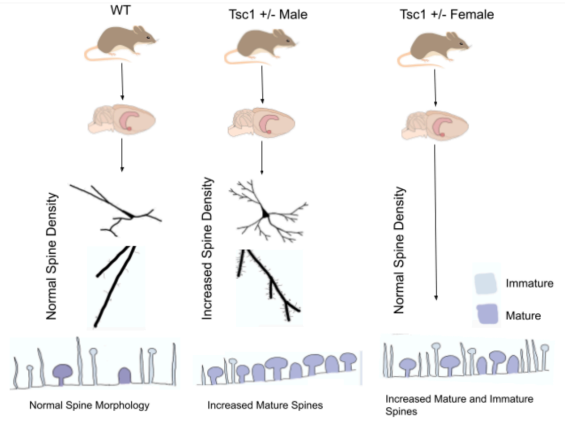


Figure- A drawn representation of the neuromorphologcal differences seen in WT, Tsc +/- male and female rats. WT rats are shown to have normal spine density and spine morphology whereas male Tsc1+/- rats have increased dendritic arbour, dendritic spine density and increased mature spine morphology compared to WT controls. Female spine density is not represented visually since this did not differ from the sex matched controls, however they are shown to have both increased mature and immature spine morphology compared to WT controls.

Other (teaching, history, outreach etc)

Crafty Cajal - Engaging Through Embroidery

Unique Code: TP001105

Authors: Jane E Haley - Edinburgh Neuroscience University of Edinburgh, Arpan Mehta - Centre for Clinical Brain Sciences University of Edinburgh, Cathy Abbott - Centre for Genomics and Experimental Medicine University of Edinburgh

Topic: Other (teaching, history, outreach etc)

As part of the engagement programme for FENS2020 in Glasgow, and to mark the centenary of the founding of the Cajal Institute in Madrid in 1920, we embarked on creating what we believe could be the world's largest Cajal-related embroidery!

Consisting of 81 separate panels representing 9 different neuron/astrocyte illustrations by Santiago Ramón y Cajal, this embroidery project was intended to engage neuroscientists, embroiderers, artists and crafters. Launched in February 2020, the project immediately had challenges to overcome as the world went into a covid-19 pandemic lockdown.

Whilst not its original intended purpose, the Cajal Embroidery Project, was found by many of our contributors to be a source of tranquility and connection during a chaotic and isolating period. It brought people together, virtually, to share progress of their work, seek advice or materials and find out more about Cajal and the project.

The pandemic resulted in the FENS Forum moving online, so we produced a short film featuring the embroideries, the process, and the contributor's feelings about the project. This was made available as one of their Open Theatre slots.

Our project has continued and, to date, we have received 77 embroideries from 64 contributors in 7 countries. The final four panels are due for completion in January 2021 and we will join all the panels together during Spring 2021 (pandemic permitting!).

The project has already generated exciting outcomes – a short article in BNA Bulletin and a published 'In Context' piece

in Lancet Neurology. During 2021, the embroideries are featuring on Lancet Neurology front covers, to accompany 'Focal point' commentaries. Plus, they will form the inaugural exhibition at the Dott Gallery within the new Division of Clinical Neurosciences building, Edinburgh.

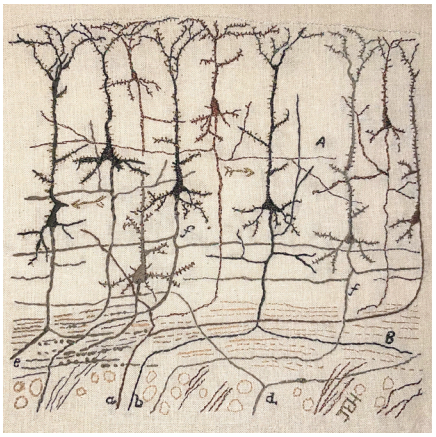
Communal crafting projects have been used by groups of women for centuries to make often beautiful but utilitarian objects. These projects have traditionally existed in the domestic sphere but we have successfully harnessed the same skills to engage not just the participants (who happened to all be women) but a wider, global community in understanding the history of neuroscience.

The Cajal Embroidery Project: celebrating neuroscience, Mehta A. et al, Lancet Neurol. 2020; 19: 979

Statistical statement: Although this project clearly involves replicants (n=9 of each image), embroideries, being an artistic expression, are not usually amenable to delivering measurable data. In addition, the end output is, by design, an n of 1. The authors feel, therefore, that statistical analysis is not appropriate or possible for this particular project.

Communal crafting projects have been used by groups of women for centuries to make often beautiful but utilitarian objects. These projects have traditionally existed in the domestic sphere but we have successfully harnessed the same skills to engage not just the participants (who happened to all be women) but a wider, global community in understanding the history of neuroscience.

The Cajal Embroidery Project: celebrating neuroscience, Mehta A. et al, Lancet Neuro



A Natural Antisense Transcript of Nitric Oxide Synthase mRNA is regulated by an endogenous micro RNA in Lymnaea Stagnalis

Unique Code: TP001275

Authors: Gabriella Taylor - Life Sciences University of Sussex, Owen Wells - Genome Damage and Stability Centre University of Sussex, George Kemenes - Life Sciences University of Sussex, Sergei Korneev - Life Sciences University of Sussex,

Topic: Other (teaching, history, outreach etc)

Introduction. Single-trial induced long term memories (LTMs) require fast removal of inhibitory memory constraints following learning. Recent findings indicate that small non-coding RNAs including miRNAs play critical roles in this process by targeting memory suppressor-encoding mRNAs. However, little is known about whether miRNAs can regulate LTM formation through the interaction with long non-coding natural antisense transcripts (long NATs). Previously, we have identified a limited pool of miRNAs, the expression of which is differentially regulated by single-trial training. Of these miRNAs, we focussed on miR-1175, which is transiently up-regulated 4h after conditioning. Perhaps the most unexpected and intriguing outcome of these studies was the discovery that miR-1175 has a putative target sequence located within a long NAT, Lym-NOS1AS. Of note, the Lym-NOS1AS is a component of the pathway activated by one-trial conditioning and is likely to act as a memory suppressor. In light of the above, here we test the hypothesis that miR-1175 negatively regulates Lym-NOS1AS expression.

Methods. We cloned a fragment of Lym-NOS1AS containing the putative miR-1175 binding site into the pSV40-GFP plasmid, downstream of a GFP ORF and upstream of a polyadenylation site. The recombinant plasmid was transfected into HEK293 cells and a cell line with stable expression of GFP/Lym-NOS1AS was generated. The cells were then transfected with either negative control mimic or miR-1175 mimic and the expression level of NOS1-AS was studied by real-time quantitative Reverse Transcription PCR.

Approach for statistical analysis. Five independent experiments were conducted and the results of quantitative experiments were analysed by using unpaired two-tailed t-tests.

Results and Conclusions. We report on the construction of a cell line with stable expression of GFP/Lym-NOS1AS. We used this cell line in our transfection experiments and demonstrate that overexpression of miR-1175 results in the decreased level of Lym-NOS1AS. Our findings indicate the existence of a regulatory pathway, which depends on the interaction between miR-1175 and Lym-NOS1AS and activation of which is required for LTM. In this pathway, miR-1175 appears to act as a trigger removing the Lym-NOS1AS memory constraint.

Ending the pain of children with severe epilepsy? An audit of the impact of medical cannabis in 10 patients

Unique Code: TP001394

Authors: Rayyan Zafar - Brain Sciences Imperial College London, Anne Schlag - Brain Sciences Drug Science/Imperial, David Nutt - Brain Science Imperial College London

Topic: Other (teaching, history, outreach etc)

Background

Scientific and anecdotal evidence suggest that whole-plant cannabis extracts are effective in reducing seizure frequency in individuals with a range of epileptic etiologies. We report a case series of 10 individuals using CBMPs in the UK to treat their conditions.

Methods

In this retrospective study, we report on patients (aged 2-48) with severe, intractable, childhood-onset epilepsies using combined cannabinoid therapy. Carers of patients provided details through the charity ‘End our Pain’ and these data were subsequently analysed. Our primary objective was to assess changes in monthly seizure frequency pre and post-initiation of CBMPs. We also report on previous and current AED, CBD: THC daily dose, quality of life, and financial costs

associated with CBMP private prescription. Change in monthly seizure frequency was assessed using a Wilcoxon Signed-ranks test.

Results
Of the 10 patients enrolled in the study, there was an 80% mean reduction in monthly seizure frequency post-initiation of CBMPs which was statistically significant (Z = 0, p < 0·01). We showed a reduction in AED use following initiation of CBMPs from a mean of 8 (±5·98) to 1 (±1·05). All patients were using either Bedrolite or Bedica (Bedrocan International) as their CBMP. Individual daily doses of THC ranged from 6·6mg – 26·5mg and for CBD, 200 mg – 550 mg. The average monthly cost of CBMP was £1816·20.

Interpretation
Our findings suggest a combination of CBD and THC-based products is effective in reducing seizure frequency in a range of epileptic conditions. We highlight the inefficacy of the healthcare system in supporting these patients who bear great personal and financial burdens. We encourage specialist physicians and relevant bodies to permit greater ease of access to these medications to those patients where efficacy has been shown.

Preregistration posters: grouped by topic

Ageing and dementia

Provoked Confabulation in people with dementia as an indication of progression of illness

Unique Code: PP001391
Authors: Angela Richards - CLCC Imperial College
Topic: Ageing and dementia

Introduction – One of the features identified in the various forms of dementia is confabulation. Many reasons have been put forward though the most compelling has been that the person genuinely believes what they have 'recalled'. This seems to be more pronounced in provoked confabulation than spontaneous confabulation.

Research question – Do individuals with dementia have an overactive default mode network (DMN) when they display provoked confabulation?

Research hypothesis – People with dementia will show significantly more activity in the DMN area compared to controls and this difference will increase with the progression of the disease.

Method: Individuals with between 1-10 years from diagnosis of dementia (main participant) and at least one family member (supporting participant) will be recruited. The family member will be asked to provide events which can be factually verified – e.g., family events (weddings, christenings, other happy events). Other exposures such as royal events, political events, sports or celebrity events will also be used. It will be ensured that whichever events are used, they were at some point known to the main participant. The main participant will then enter the fMRI machine. The researcher will ask the main participant about the relevant events, either by talking to them freestyle (recall) without prompts or using prompts (recognition, e.g., pictures). The researcher will ask the main participant what they remember, if any, about the event. There will also be a matched control group who do not have any cognitive problems.

They will first be asked to recall events as they remember them. They will then be asked to confabulate as best as they can about those events, and this will also take place in the fMRI machine. Both groups of participants will be assessed using a dementia screening tool such as the Montreal Cognitive Assessment (MoCA) Test for Dementia. The primary focus will be on the DMN, though a few other relevant areas will also be considered (e.g., entorhinal cortex and hippocampus).

Analysis: This will be done by comparing activity on the DMN including the hippocampal formation between the main participants and control group. There will also be some attempt to see if there are higher levels of default mode activity depending on the years from initial diagnosis, and to see if there are any patterns in the confabulation – e.g., always including characters with the same name. MANOVA: IV1 – Confabulation: (1) Provoked, (2) non-provoke; IV2 – Dementia diagnosis: (1) Mild, (2) moderate, (3) severe; (4)no diagnosis/ no signs of dementia; IV3 – Duration of diagnosis: (1) up to 1 year, (2) 1-2 years, (3) 3-4 years, (4) 5 years plus; IV4 - Category of participant: (1) young onset (pre-65 years), (2) young old (65 -74), (3) mild old (75-84), (4) later old (85+). DV1: Score on Montreal Cognitive Assessment (MoCA) Test for Dementia; DV2 – Activation level of DMN; DV3: Activation level of hippocampus network: DV4: Activation level of entorhinal cortex.

Expected result: Participants with dementia show more activity in their default mode network when recalling events that demonstrate provoke confabulation that those who do not have dementia.

Clinical implications/conclusions: Perhaps this study can go some way to helping clinicians to identify difficulties that individuals with dementia have with recalling salient events. Family members and friends of a person affected by dementia could be trained to understand confabulation as a biological condition and not a deliberate attempt to deceive. Some consideration will also be given as to whether asking such individuals questions in different ways may help them achieve better recall or recognition.

Immunohistochemical and electrophysiological investigation of E/I balance alterations in animal models of frontotemporal dementia

Unique Code: PP001069

Authors: Katie Hill - School of Psychology and Computer Science University of Central Lancashire, Martin Clark - School of Psychology and Computer Science University of Central Lancashire

Topic: Ageing and dementia

Behavioural variant frontotemporal dementia (bvFTD) is a neurodegenerative disease characterised by changes in behaviour. Apathy, behavioural disinhibition and stereotyped behaviours are the first symptoms to appear and all have a basis in reward and pleasure deficits. The ventral striatum and ventral regions of the globus pallidus are involved in reward and pleasure. It is therefore reasonable to suggest alterations in these regions may underpin bvFTD. One postulated contributory factor is alteration in E/I balance in striatal regions. GABAergic interneurons play a role in E/I balance, acting as local inhibitory brakes, they are therefore a rational target for research investigating early biological predictors of bvFTD.

To investigate this, we will carry out immunohistochemical staining for GABAergic interneurons (parvalbumin and neuronal nitric oxide synthase) in striatal regions of brains taken from CHMP2B mice, a validated animal model of bvFTD. We hypothesise that there will be fewer GABAergic interneurons in the striatum which may lead to 'reward-seeking'

behaviour in bvFTD. This will also enable us to investigate any preclinical alterations in interneuron expression within this region. Results will be analysed using a mixed ANOVA and if significant, post hoc t-tests will be used. The second part of our study will involve extracellular recordings from CHMP2B mouse brains using a multi-electrode array (MEA). This will enable us to determine if there are alterations in local field potentials (LFP) in preclinical and symptomatic animals. We will also be able to see if neuromodulators such as serotonin and dopamine effect LFPs after bath application. We will develop slice preparations to preserve pathways between the ventral tegmental area and the ventral pallidum, an output structure of the striatum, and the dorsal raphe nucleus and the VP. Using the MEA we will stimulate an endogenous release of dopamine and serotonin using the slice preparations as described above. This will enable us to see if there are any changes in LFPs after endogenous release of neuromodulators. We hypothesise there will be an increase in LFPs due to loss of GABAergic interneurons.

Alzheimer's disease related changes in cell types of the limbic thalamus and effects on in vivo neuronal activity

Unique Code: PP001097

Authors: Barbara Sarkany - Department of Pharmacology University of Oxford

Topic: Ageing and dementia

Alzheimer's disease (AD) is the most prevalent form of dementia. The hallmarks of AD are abnormally folded amyloid-beta and tau proteins (Goedert et al 1995). While the cerebral cortex remains a major focus of AD research, the role of the thalamus has received less attention. Evidence of its importance is highlighted by pathological tau (p-tau) inclusions in specific 'limbic' nuclei of the thalamus (Braak and Braak 1991). These proteins might disrupt thalamic neuronal activity, leading to cognitive deficits. Our goal is to define human thalamic cell types that are most vulnerable in AD and relate these to in vivo neuronal activity of corresponding mouse cell types.

To identify vulnerable cell types in AD we will perform immunohistochemistry in sections of anterior thalamus from donors that had different Braak tangle stages. Immunoreactivity for at least one molecular marker will be used to define different subpopulations in combination with an antibody against p-tau. Subpopulations will be compared with those from a transgenic mouse line that expresses p-tau. To make predictions about the effects of tau pathology on neuronal activity in humans, we will record network and single neuronal activity in awake mice during different behavioural states. After recording, neurons will be labelled with neurobiotin for post hoc identification of axons, molecular profiling and localization of pathological tau.

In order to analyse affected neurons in the limbic thalamus, samples will be collected from cases at the same Braak stages (n=4 stage I-II, n=4 stage V-VI) along with age and sex matched neurologically normal cases (n=4). Proportions of cell subpopulations will be quantified in 3 sections/case. Relative numbers of different cell types that are affected by the pathology will be calculated. To establish whether there are changes in coupling between the limbic thalamus and temporal cortex, network oscillations and single neuronal activity will be measured in transgenic and non-transgenic littermates (n=6 mice per group). Coherence tests and the Rayleigh test of uniformity will be used. Mean firing rates will be pooled per region per animal to avoid pseudoreplication.

Braak and Braak(1991) Acta Neurop. 81(3):261-8
Goedert et al(1995) Neurosci lett. 189(3):167-9

Understanding the pathological mechanisms of secondary damage after traumatic brain injury

Unique Code: PP001120

Authors: Katerina Palios - Basic and Clinical Neuroscience King's College London, Professor Elizabeth Bradbury - Wolfson Centre for Age-related Diseases King's College London, Dr Claire Troakes - Basic and Clinical Neuroscience King's College London

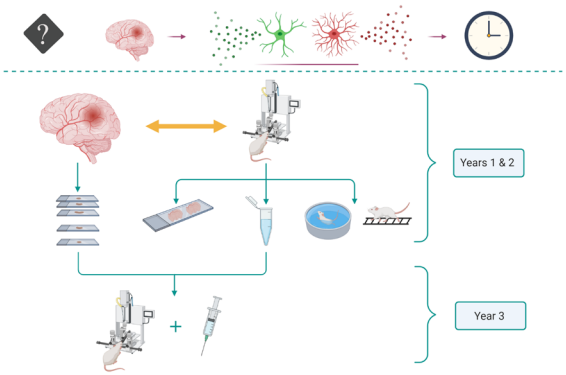
Topic: Ageing and dementia

Background: Despite advances in our mechanistic understanding of the secondary injury after traumatic brain injury (TBI), treatment strategies remain limited. For some, the secondary injury may initially appear subclinical but manifests later in life as neurodegenerative disease. Chronic activation of both the complement system and glia is associated with TBI and neurodegeneration, suggesting a shared pathology across the two conditions and an opportunity for therapeutic intervention. The timing of complement activation after trauma appears critical in determining its relative neurotoxic or neuroprotective qualities. Clusterin is a complement inhibitor that may play a role in TBI-related neurodegeneration. We recently demonstrated a biphasic pattern of clusterin expression in TBI patients with survival times ranging from 30 minutes to 9 months. However, complement expression and its role in mediating the glial response has not been fully characterised after TBI.

Aim: The present study aims to delineate the spatial and temporal localisation of complement factors and glia after TBI and will combine human and rodent data. Therapeutic interventions modulating the inflammatory response will then be developed and tested in rats.

Methods: We will evaluate expression of complement factors and astrocyte subtypes in severe TBI patient tissue with survival times ranging from 30 minutes to 16 years, focusing on contusion sites and white matter regions. We will also use a moderate-severe rodent model of controlled cortical impact (CCI) to provide histological, biochemical, and behavioural data from acute to chronic time points post-injury for direct comparison with human data and to enable more specific temporal and spatial analysis. Mapping the inflammatory response to TBI in both human and rodent tissues will allow the identification of potential pharmacological interventions to be tested in the CCI model.

Statistics: Histological and biochemical data will be analysed by one-way ANOVA, with appropriate post-hoc multiple comparison corrections. Levels of inflammatory markers will be assessed at various post-injury time points and compared to controls. Functional data will be analysed by a two-way repeated measures ANCOVA where baseline performance is a co-variate.



The effects of healthy ageing on glial cells in the rat spinal cord dorsal horn

Unique Code: PP001128

Authors: Aerin Thompson - Medicine and Health Sciences University of Nottingham, Victoria Chapman - Medicine and Health Sciences University of Nottingham, Gareth J Hathway - Medicine and Health Sciences University of Nottingham, Stephen G Woodhams - Medicine and Health Sciences University of Nottingham, Li Li - Medicine and Health Sciences University of Nottingham, Emma Battell - Medicine and Health Sciences University of Nottingham

Topic: Ageing and dementia

Introduction

Glial cells play vital roles in normal and pathological processes, including the induction and maintenance of pain states. Ageing leads to greater susceptibility to pain states, but little is known about changes in the number and activation state of glial cells may contribute to this. To determine how healthy ageing affect glial cells in the key pain processing hub of the spinal cord dorsal horn (DH) this study will employ immunohistochemistry (IHC) to compare markers of astrocytes and microglial cells in young adult and ages rats.

Methods

40um sections of L5-6 lumbar spinal cord from aged (18-24 months, n=4) and young adult (2-3 months, n=4) male Sprague Dawley rats will be cut on a freezing microtome. 6-8 spinal sections per animal will be immunolabelled for markers of glial cells via established IHC protocols. Non-specific binding will be blocked via incubation in phosphate buffer saline (PBS) containing 5% donkey serum, with 0.3% Triton X-100 for tissue permeabilisation. Sections will be incubated with primary antibody solution of PBS, 5% donkey serum containing GFAP (rabbit, Z0334) to label astrocytes and IBA1 (goat, NB100-1028) to label microglia, both a 1:1000 dilution. Subsequent incubation with donkey anti-rabbit 488 (A21206) and donkey anti-goat 594 (A11058), both 1:500 dilution. Cell nuclei will be labelled via brief incubation with DAPI (1:500 in PBS) to enable total cell counts and delineation of laminar boundaries. All sections will be mounted onto gelatinised slides and cover-slipped using fluromount.

Slides will be imaged on a Zeiss 200M microscope using DAPI, FITC, and TRITC filter sets, focusing on the superficial DH. ImageJ will be used to view and analyse immunolabelling. To control for autofluorescence and non-specific labelling, sections from each individual will be processed in parallel with primary antibodies omitted.

Approach for statistical analysis

Images from 3-4 sections per animal will be collected at 10x and 20x magnification to assess microglial and astrocytic number and morphology. Total cell counts, cell density, laminar distribution, and labelling intensity for each marker will be the primary outcomes. Statistical comparison between groups will be via Mann-Whitney U tests or T-tests, as appropriate.

Protocol for a remote data collection speech analysis study in people at risk for Alzheimer's disease dementia: The SPeAk study

Unique Code: PP001139

Authors: Sarah Gregory - Edinburgh Dementia Prevention, Centre for Clinical Brain Sciences University of Edinburgh, Nicklas Linz - KI Elements KI Elements, Kai Langel - Janssen Clinical Innovation Janssen ,Hannah Pullen - Edinburgh

Dementia Prevention, Centre for Clinical Brain Sciences University of Edinburgh, Dr Alexandra König - National Institute for Research in Computer Science and Automation (INRIA) National Institute for Research in Computer Science and Automation (INRIA),Dr Saturnino Luz - Centre for Medical Informatics University of Edinburgh, Professor John Harrison - Multiple 1 Metis Cognition Ltd, Kilmington Common, UK 2 Alzheimer Center Amsterdam, Department of Neurology, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands 3 Institute of Psychiatry, Psychology ,Professor Craig Ritchie - Edinburgh Dementia Prevention, Centre for Clinical Brain Sciences University of Edinburgh
Topic: Ageing and dementia

Introduction: Speech and language analysis is an emerging area of research in the identification of Alzheimer's disease (AD) biomarkers (Boschi et al, 2017). Such biomarkers include failure to stop autocorrect errors when reading aloud, which correlates with Aβ1-42 (Gollan et al, 2020). This study aims to develop algorithms to identify speech biomarkers in the data that are predictive of CSF AD biomarkers. Secondary and exploratory objectives are to assess ceiling performance and test-retest reliability of the phone administered cognitive assessments, to explore participant acceptability and to conduct conversational analysis. Methods: Participants must have previously enrolled in the EPAD LCS or CHARIOT Pro sub-study at the Edinburgh Dementia Prevention site and agreed to be contacted about future research. Consent will be recorded using a secure online form. We will collect demographic information (age, sex, education, living status and medication). Participants will initially engage in two conversational tasks followed by immediate and delayed list learning, digit span, semantic and phonemic fluency. Participants will repeat the cognitive testing at 3 months with an automated tester. Participants will receive acceptability questionnaires after each appointment. Participants will be randomised 1:1 to receive results after each visit or only at study completion. Approach for statistical analysis: Algorithm development will extract the following features: classical cognitive outcome variables, novel or qualitative outcome variables based on produced language and low-level speech descriptors such as speech rate. A combination of predictive statistical and machine learning models will be used, with participants' biomarker status (from EPAD LCS) as a target variable. Models will be constructed with task specific features and using aggregated variables spanning multiple cognitive tasks. Ceiling and test-retest reliability with be analysed with ANOVA and repeated measures correlation. Frequency statistics, paired t-tests and qualitative analysis will be used for acceptability questionnaires. Exploratory conversational analysis will look at the spontaneous speech for features such as turn taking.

Protein Interactors of the Alzheimer's Disease-Associated Microglial Protein ABI3

Unique Code: TP001201
Authors: Catherine Widnall - Dementia Research Institute Cardiff University, Professor Derek Blake - MRC Centre for Neuropsychiatric Genetics and Genomics Cardiff University, Christopher Smith - Dementia Research Institute Cardiff University, Dr Matthew Hill - Dementia Research Institute Cardiff University
Topic: Ageing and dementia

Alzheimer's disease (AD) is a neurodegenerative disorder currently affecting over 5% of the global population over the age of 60, with no curative care. Susceptibility loci have been identified using genome-wide association studies, and exome genotyping has identified rare coding variants associated with AD risk. One such risk gene is ABI3. ABI3 is highly expressed in microglia, but its specific biological function is unknown. However, it is understood to form part of the WAVE regulatory complex (WRC). The WRC regulates the cytoskeleton via actin polymerisation, therefore ABI3 is likely to influence microglial motility and morphology. Disruption to these functions may influence risk for AD via the ability of microglia to migrate to and phagocytose amyloid plaques. To investigate the function of ABI3 in an unbiased fashion, we

will use the proximity labelling method BioID coupled with mass spectrometry to identify its protein interactome in microglia-like cells. ABI3 interacting proteins will be identified by filtering against a negative control and analysed using SAINTexpress. These results will be presented here. The identification of these interactors will be important for elucidating the biological function of ABI3, laying the groundwork to understand the contribution of ABI3 coding variants in AD.

Exploration of synergistic and redundant information interactions with cognitive reserve in the ageing brain using fMRI and MEG big data

Unique Code: PP001219

Authors: Jennifer C. Fielder - Department of Psychology University of Cambridge, Pedro A. M. Mediano - Department of Psychology University of Cambridge, Fernando E. Rosas - Department of Brain Sciences; Data Science Institute; Centre for Complexity Science Imperial College London, Daniel Bor - Department of Psychology University of Cambridge

Topic: Ageing and dementia

Introduction: The degree of neuropathology in the ageing brain does not correlate well with the degree of cognitive decline. This is explained by 'cognitive reserve,' a compensatory mechanism to overcome stressful conditions such as ageing, dementia, or drowsiness. However, it is not yet well known how cognitive reserve is instantiated in the brain. One related finding used partial information decomposition (PID), a field within information theory, to decompose fMRI data into redundant (each variable represents the same information) or synergistic (information adds up to more than the sum of its parts) components: Preliminary evidence suggests that the brain becomes more redundant with age, especially in prefrontal and motor cortices, thus affecting basic functions such as working memory, executive and motor functions (Gatica et al., 2020). Methods: The Cambridge Centre for Ageing Neuroscience (CamCAN) dataset enables us to combine PID and cognitive reserve in the ageing brain, replicate this preliminary result in fMRI and extend it in a new modality, magnetoencephalography (MEG), in a large dataset (n=650), thus enabling us to examine effects with higher temporal resolution in a robust way. Analysis: We will operationalise high cognitive reserve here as ability to maintain performance while drowsy (measured neurally) on the CamCAN Go/NoGo task, an attentionally demanding response inhibition task. We will use bespoke PID analysis methods applied to MEG and fMRI data. This includes 'O-information' which quantifies whether information is redundant (positive value) or synergistic (negative value), and 'S-information', which quantifies the overall strength of interdependencies. We hypothesise that in both fMRI and source localised MEG, we will find greater redundant information (positive O-information), especially in prefrontal cortex, and greater interdependencies between brain regions (greater S-information) in older participants, in line with the previous study. Furthermore, we predict that higher cognitive reserve will be correlated with reduced redundancy, and greater synergy, especially in the prefrontal-parietal network, and reduced interdependencies between brain regions.

Systemic vascular health and region-specific neurovascular coupling in older adults

Unique Code: PP001274

Authors: Gabriella MK Rossetti - Centre for Integrative Neuroscience and Neurodynamics University of Reading,Jonathan M Gibbins - Biomedical Sciences, Institute for Cardiovascular and Metabolic Research University of Reading, Julie A Lovegrove - Human Nutrition, Institute for Cardiovascular and Metabolic Research University of Reading, Anastasia Christakou - Centre for Integrative Neuroscience and Neurodynamics University of Reading

Topic: Ageing and dementia

Introduction
Cardiovascular and metabolic health conditions including hypertension, heart disease, and diabetes are associated with neurodegeneration in older life. In particular, vascular risk factors are associated with structural and functional impairments in the posterior cingulate cortex (PCC), and impaired PCC-dependent episodic memory performance. However, through what mechanism systemic vascular health causes these effects, and why the PCC appears disproportionately affected. “Vascular health” is typically classified based on the presence or absence of clinical diagnosis, but studies rarely measure physiological components. In particular the balance of contribution between cerebrovascular, neural, and neurovascular coupling (NVC) remains to be clarified. This study will investigate these relationships across physiological and functional levels: from cellular vascular signalling, through systemic vascular function, to region-specific cerebrovascular and neuronal health, and NVC.

Methods
Fifty individuals aged 50+ years will be recruited. We will conduct assessments of in vitro vascular signalling including assessments of haemostatic function in combination with in vivo systemic vascular function assessed by laser Doppler imaging. Cerebrovascular function will be assessed using ASL to measure cerebral blood flow (CBF) at rest, and in response to a hypercapnic challenge to asses cerebrovascular reactivity (CVR). MRS (MEGAPRESS) will provide a measure of GABA+ concentrations to indicate neuronal health. Neurovascular coupling will be assessed by BOLD fMRI during cognitive tasks. NVC in the PCC will be determined during episodic memory recall and compared to NVC in visual cortex during a checkerboard task.

Approach for statistical analysis
NVC will be analysed by a combination of general linear model (GLM) analysis and deconvolution analysis within a priori PCC and visual cortex ROIs. Deconvolution analysis does not assume the canonical heamodynamic response function (HRF), allowing for estimation of the region-specific HRF. We will use linear mixed effects modelling to test the relationships between systemic vascular function and cerebral outcomes, and compare the strength of these relationships between the PCC and visual cortex.

Investigating the impact of M1 muscarinic acetylcholine receptor activation on electrophysiological markers of terminal neurodegenerative disease

Unique Code: PP001297
Authors: Jessica Bowden - Centre for Translational Pharmacology University of Glasgow, Dr Sophie Bradley - Centre for Translational Pharmacology University of Glasgow, Dr Keith Phillips - Lilly Research Laboratories Eli Lilly, Professor Andrew Tobin - Centre for Translational Pharmacology University of Glasgow
Topic: Ageing and dementia

Activating the cholinergic system is a major therapeutic approach for Alzheimer's disease, but a lack of selectivity limits the efficacy of current treatments. Our lab has shown that directly targeting the M1 muscarinic acetylcholine receptor (mAChR) can ameliorate behavioural deficits and slow progression of prion-mediated neurodegeneration1. The prion disease model recapitulates several features of Alzheimer’s disease, including memory deficits and progressive neuronal loss leading to terminal disease. The study proposed here will apply in vivo electrophysiology to the prion disease model. We will record from the same animals over several weeks to (i) establish how and when electrophysiological signals change in this mouse model, and (ii) examine the effects of daily dosing of compounds which activate or potentiate the M1 mAChR on electrophysiological signals.

In this study, six-week-old mice will receive intracerebral inoculation of prion disease brain homogenate or normal brain homogenate. After a recovery period of at least two weeks, mice will be implanted with recording electrodes, consisting of seven skull screws. After a further recovery period, weekly recordings will be made in the animal's home cage using the Taini wireless transmitter system. A subset of prion and control mice will receive daily doses of an M1 mAChR compound or vehicle from seven weeks post-inoculation. The Chronux toolbox in MATLAB will be used to generate power spectra. The FOOOF algorithm2 will be applied to these spectra to distinguish spectral peaks from aperiodic components.

We will compare outputs of the FOOOF algorithm over the course of the disease within each subject and between the prion and control inoculated groups. This will include the aperiodic exponent and offset, and the frequency and amplitude of the major peak. If a peak is not extracted, power spectra with the aperiodic component removed may be analysed instead. We plan to use a bootstrap approach for statistical analysis, with cluster-based multiple comparisons correction where appropriate.

1 Bradley et al. (2017) J Clin Invest.
2 Donoghue et al. (2020) Nat Neurosci.

Understanding the genetic contribution to neuroinflammatory cell traits using iPSC-derived microglia

Unique Code: PP001309

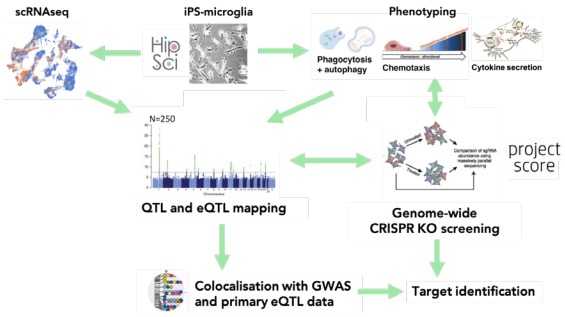
Authors: Marta Perez-Alcantara - Wellcome Sanger Institute Wellcome Research Campus, Yixi Chen - Wellcome Sanger Institute Wellcome Research Campus, Sam Washer - Sir William Dunn School of Pathology University of Oxford, Juliette Steer - Wellcome Sanger Institute Wellcome Research Campus, Daniel Ebner - Target Discovery Institute, Nuffield Department of Medicine University of Oxford, Sally Cowley - Sir William Dunn School of Pathology University of Oxford, Gosia Trynka - Wellcome Sanger Institute Wellcome Research Campus, Andrew Bassett - Wellcome Sanger Institute Wellcome Research Campus,

Topic: Ageing and dementia

There is mounting genetic evidence, both from common and rare variants, that implicates microglia in neurodegenerative disease. Microglia perform various immunological functions in the brain as sentinels, housekeepers and mediators of neuroinflammatory response: these include cellular signalling, migration and phagocytosis. Our aim is to assess how these cellular functions might be perturbed in neurodegenerative disease (particularly Alzheimer's but also Parkinson's, amyotrophic lateral sclerosis and frontotemporal dementia), and the genetic contribution to these phenotypes. To achieve this, we will examine the role of neurodegeneration-associated variants and loci in the gene expression and cellular phenotypes of iPSC-derived microglia differentiated in vitro.

We will perform pooled differentiations towards microglia of iPSCs from ~250 donors from the human pluripotent stem cell initiative (hipSCi), as well as candidate gene KOs and disease relevant mutant lines on isogenic background. This will be followed by phenotyping (for functions such as phagocytosis and chemotaxis) and single cell RNA-seq (scRNA-seq) to assess gene expression. Finally, we will perform expression and phenotypic Quantitative Trait Locus (QTL) mapping and colocalization with common variants identified by genome-wide association studies of neurodegenerative traits, with the aim of linking these variants to their target genes.

We are improving the in vitro microglia maturation protocols to achieve cells more phenotypically and transcriptomically similar to primary microglia. Phenotyping protocols are adapted for pooled designs (10-20 donors/pool) e.g. with FACS-based outcomes and sequencing that allows donor identity recovery for phenotypic QTL analysis. Expression QTL analysis of pooled microglia (using established methods such as tensorQTL) will be performed on scRNA-seq from microglial subpopulations under resting and stimulated (e.g. with LPS) conditions, to map the transcriptomic changes that occur during immune response. Barcoding with gRNAs will also permit pooled differentiation of disease-relevant mutants on isogenic background. Finally, a subset of phenotypic assays will be applied to a genome-wide CRISPR screening to identify more genes involved in microglial processes.



INVESTIGATING THE ROLE OF SLEEP DISTURBANCE IN AMYLOID CO-PATHOLOGY IN DEMENTIA WITH LEWY BODIES

Unique Code: PP001322

Authors: Katherine Lloyd - Institute of Clinical Neurosciences University of Bristol, Elizabeth Coulthard - Associate Professor in Dementia Neurology University of Bristol

Topic: Ageing and dementia

Introduction

There is a complex and likely bidirectional relationship between sleep and amyloid-β pathology in the central nervous system. Sleep disturbances precede cognitive symptoms in Alzheimer's disease (AD) and are associated with greater markers of amyloid-β (1). Although an alpha-synucleinopathy, more than 50% of patients with Dementia with Lewy Bodies (DLB) have co-pathology with amyloid-β (2). There is growing evidence that amyloid-β produces a more severe phenotype of DLB (3). Sleep disturbance is common in DLB but its relationship with amyloid-β co-pathology has not been established. In this pilot study, we will test the hypothesis that greater sleep disturbance in DLB predicts the presence of amyloid-β co-pathology.

Methods

We will recruit patients with a diagnosis of probable DLB from a cognitive disorders clinic in the South West of England. Amyloid-β status will be determined by CSF analysis of Amyloid-β 42:40 and patients will be classified into Aβ+ or Aβ-. Clinical data will include sleep assessments (Pittsburgh Sleep Quality Index, REM sleep behaviour screening questionnaire, EEG) and cognitive performance.

Approach for statistical analysis

We will first define the demographic and clinical characteristics by amyloid-β status. For each sleep assessment we will use logistic regression to investigate the differences in domains of sleep disturbance according to amyloid-β status in

DLB patients.

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Circuit dynamics and oscillations

The Development of Functional Neuronal Network Models of Complex Decision-Making

Unique Code: PP001263

Authors: Gemini Katwa - Business, Law and Social Sciences (School of Psychology) Birmingham City University

Topic: Circuit dynamics and oscillations

Introduction

At the macroscale, determining the connectomics of structural and functional/dysfunctional neuronal connectivity in cortical/inter-regional pathways of complex decision-making currently remains unidentified. This is perhaps an urgent and simultaneously least explored and area of research prioritisation. Investigating neurotypical, schizophrenia and those with psychopathic traits, this research aims to expose underlying structural and functional/dysfunctional neuronal networks in decision-making, and its associations to behavioural and clinical symptomology.

Methods

Participants will complete the general decision-making style questionnaire (GDMS; Scott & Bruce, 1995), Wechsler Adult Intelligent Scale (WAIS-IV; Weschler, 2008) and Psychopathic Traits Scale (PPTS; Boduszek et al., 2016). The neurophysiological response to decision-making tasks: Iowa Gambling Task (IGT) and Flanker Task (FT) will be recorded using electroencephalogram (EEG) and event-related potential (ERP) methodology, to obtain functional data corresponding to neuronal connectivity in inter-regional pathways.

Approach for Statistical Analysis

ERP data will be statistically analysed where the research will look for a main effect or an interaction in a crossed factorial design, and ANOVA-based statistical analysis will be the dominant approach. ERP data will be visualised in the ERP waveforms (ActiView; Biosemi, Netherlands) and will be analysed using MATLAB ToolBox 2019b (MathWorks, USA) to define the amplitudes and latencies for P300 and N2. Graph theory measures and exploration of small-world networks will determine and map the functional neuronal networks involved in complex decision-making. A neurotypical sample is expected to reveal high positive scores in decision-making tasks, with optimal prefrontal neuronal and inter-regional pathway activity, indicating a ‘normal’ baseline for functional neuronal decision-making connectivity. In contrast, schizophrenia and psychopathic traits samples are expected to reveal high negative scores in decision-making tasks and ERP amplitude and latencies relating to aberrant functional neuronal connectivity, therefore indicating dysfunctional decision-making and possible explanations to the manifested behavioural/clinical symptoms.

Cognition and behaviour

Heartbeat Evoked Potential modulation by emotion, expertise, autism and personality characteristics

Unique Code: PP001058
Authors: Vasiliki Meletaki - Psychology Department City, University of London
Topic: Cognition and behaviour

The heartbeat evoked potential (HEP) has been often used as a neural marker of cardiac or visceral activity more generally. Growing empirical evidence suggests that the heart and HEP as a cortical marker play a critical role in visual perception, emotion and consciousness more broadly supporting embodied cognition theories (e.g. Park and Blanke, 2019). Previous studies from our lab provided strong evidence for group effect comparing professional dancers vs control participants and participants with ASD diagnosis vs controls on visual and embodied emotion processing by means of visual and somatosensory evoked potentials respectively (Fanghella et al., in prep. and Meletaki et al., in prep.). In all experiments, neural responses to facial expressions (faces with happy, fearful and neutral expression) were measured. Their electrophysiological activity (EEG) and electrocardiogram (ECG) were recorded and their levels of alexithymia, stress (state and trait), body awareness and depression were collected (employing the questionnaires: TAS-20, STAI-S, STAI-T, MAIA and DBI). In the present study, we aim to look firstly, how emotion and personality traits interact with HEP and secondly, how theses dynamics are modulated on different populations (professional dancers, participants with ASD and control participants). Repeated measures ANOVA will be used to investigate group and emotion effect and regression and correlational analyses to investigate potential modulation by personality traits. This study aims to contribute to the HEP and brain-viscera interaction literature offering valuable evidence on how visual emotion, expertise, autism and personality characteristics may modulate the HEP.

Exploring the effects of global context on event boundary strength in naturalistic events

Unique Code: PP001088
Authors: Verity Smith - MRC Cognition and Brain Sciences Unit Cambridge University, Richard Henson - MRC Cognition Brain Sciences Unit Cambridge University, Aya Ben-Yakov - MRC Cognition and Brain Sciences Unit Cambridge University
Topic: Cognition and behaviour

Event boundaries serve as an organising principle for long term memory. One commonly observed finding is that the order of occurrences within the same event are better remembered than the order of occurrences separated by a boundary (DuBrow and Davachi 2014; Heusser et al. 2018).

However, it is unknown how characteristics of the boundary relate to its effect on memory. For example, does the strength of an event boundary affect memory, and what determines boundary strength? We aim to answer these questions with a series of experiments using naturalistic stimuli from the simulated game environment “The Sims 4”.

Three groups of participants will be shown movies, made up of a series of pictures, depicting the everyday lives of Sims characters. For the baseline group (group 1), there will be a gradual transition between two characters, and we will test the effect of boundaries within/across events in the same character. To create a stronger boundary, for group 2, there will be jumps between characters and we will test across events of different characters. To examine the effect of strong boundaries when intermixed with weaker ones, for group 3, there will also be jumps between characters, but we will test how that affects the boundaries within character.

All statistics will be calculated using the BayesFactor package, ttestBF (Morey et al. 2018) for Bayes factor calculations in R. First, in the baseline group, we aim to replicate the boundary effects on temporal order memory with a one-tailed, paired t-test. For an effect of boundary strength, we will use a one-tailed unpaired t-test to test if boundary effects are stronger in group 2 than group 1. To see whether boundary strength is influenced by the presence of stronger boundaries, we will use a one-tailed unpaired t-test to test if boundary effects are stronger in group 1 than group 3.

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Heusser AC, Ezzyat Y, Shiff I, Davachi L. 2018. Perceptual boundaries cause mnemonic trade-offs between local boundary processing and across-trial associative binding. J Exp Psychol Learn Mem Cogn

Morey D, Rouder JN, Jamil T. n.d. Bayes factor: Computation of Bayes factors for common designs (R package version 0.9.12)

Examining movement kinematic differences in Autism Spectrum Disorder and Parkinson's Disease: a matched-groups comparison study

Unique Code: PP001093

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Topic: Cognition and behaviour

A growing body of research has demonstrated differences in movement kinematics between autistic and non-autistic individuals, such as a jerkier movement profile in autism (Cook et al., 2013). Similarly, evidence from individuals with Parkinson's Disease (PD) has demonstrated increased jerk in movement kinematics (Alberts et al., 2000). However, these studies show a distinction in the speed of movements, where higher values were observed in autism but lower values in PD relative to controls. In light of reports of an increased prevalence of PD in the autistic population (Starkstein et al., 2015), it is important to quantify the extent of overlap in movement characteristics of the two conditions. Such overlap may be responsible for increased rates of diagnosis given that PD is primarily assessed using tasks of motor function.

This study will compare 3 groups of age, IQ and gender matched participants: autistic individuals (ASD), individuals with PD (both on and off dopaminergic medication) and control participants (CTRL). To index kinematics, participants will trace particular shapes, that have a highly predictable relationship between speed and curvature in the general

population (Huh & Sejnowski, 2015), on a touchscreen device. Kinematic parameters of jerk and speed will be extracted from participants' recorded movements for each shape. A beta value will also be calculated to index how participants modulate their speed as a function of each shapes' curvature. Linear mixed models will be employed for each kinematic parameter with group, shape, and group-shape interaction as fixed effects. Random intercepts will be included for trial number to account for fatigue or practice effects, and participant number.

We anticipate increased jerk for both the ASD and PD-OFF groups relative to the PD-ON and CTRL groups. Similarly, we expect differences in beta values for both former groups, such that they show steeper decreases in speed for curves relative to straights within shapes. However, we hypothesise a difference between these groups in terms of speed, where we expect increased speed in the ASD group and decreased speed in the PD-OFF group relative to the PD-ON and CTRL groups. This study will be the first to present such findings in a matched-groups design.

Do Inhibition and Visuo-Spatial Function Influence Non-symbolic Magnitude Processing in Parkinson's Disease?

Unique Code: PP001141

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Topic: Cognition and behaviour

A prominent theory assumes that the approximate number system (ANS), which is thought to be measured by non-symbolic magnitude comparison tasks, constitutes the basis for development of numerical skills. Recent studies showing influences of inhibition and visual strategies raise the question of what is measured with this task. Elderly people show age-related inhibitory decline, which can be intensified in Parkinson's disease (PD) where inhibitory and visuo-spatial deficits occur. Therefore, PD-immanent inhibitory and visuo-spatial deficits in some patients allow for a quasi-experiment studying the influence of these cognitive domains on the performance in a typical ANS task. This enables the inference of conclusions for the theory of number processing from this clinical population. Consequently, we want to address the questions (H1) do PD patients with and without inhibitory and visuo-spatial deficits differ in the ANS task? and (H2) how do these cognitive domains influence the relationship with arithmetic?

The sample will consist of 60 PD patients with and without mild cognitive impairments.

Numerical tests comprise of non-symbolic comparisons of dot arrays (congruency of visual dimensions with numerosity; ratios 1:2, 3:4, 5:6, and 7:8) and arithmetic tasks (4 basic arithmetic operations).

Clinical measures will consist of motor symptoms (UPDRS-III), depression (BDI-II), cognitive status (assessed with MoCA < 26), inhibition (TAP go/ no go "2 out of 5") and visuo-spatial function (Benton Line Orientation Test).

The primary outcomes will be accuracy and reaction time (RT) for ANS, amount of errors in inhibition, sum score of visuo-spatial function, and sum score of mental arithmetic.

Data pre-processing will be model-based with respective necessary transformations. Performance in clinical measures will be correlated with numerical tests to identify possible confounders so that for hypothesis testing, linear mixed models with respective fixed (cognitive status, inhibitory deficit, visuo-spatial deficit) and random (participants, respective confounders) effects will be conducted for H1. Additionally, multiple regression analyses will be conducted for H2 to compare the relationship between performance in ANS task and arithmetic task across the samples.

Is the right intraparietal sulcus critical for driving brain-wide focus on task-relevant information?

Unique Code: PP001144

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Topic: Cognition and behaviour

Adaptive coding in the frontoparietal multiple demand (MD) network is proposed to facilitate performance on a range of cognitive tasks by selectively prioritising task relevant information (Duncan, 2013). One of these regions, the intraparietal sulcus (IPS), has been linked to both spatial and feature-based attention (Bettencourt & Xu, 2016), and its disruption with TMS can lead to failures in object identification and comparison (Beck et al., 2006). Here we ask whether information coding in the IPS is critical for driving brain-wide focus on task-relevant information, using the powerful combination of TMS with multivariate pattern analysis (MVPA) of fMRI data.

Participants will attend two experiment sessions. In session 1, we will acquire MRI functional localisers (IPS, LOC, and BA1718), and a detailed structural scan. In session 2, we will record TMS-fMRI data using two 7-channel TMS-dedicated surface coils (de Lara et al., 2015). Participants will complete an object categorisation task (figure 1), during which single TMS pulses will be delivered to the right IPS at either active (110% motor threshold) or control (40%) intensity. TMS pulses will be delivered 90 ms after the onset of the stimuli (Koivisto et al., 2012; 2014), using an interslice TMS-fMRI sequence. We will use MVPA of the fMRI data to investigate the effect of active TMS on the coding of attended and unattended objects in the MD network (ACC, IPS, DLPFC, VLPDC) and occipital cortex (V1, LOC), during high and low perceptual load. If rIPS is critical for facilitating coding of relevant information in the MD network during high load, we expect to see a decrease in task performance and a reduction in MD coding of attended objects for active TMS compared to control. If rIPS also has a causal top-down role, we predict a similar reduction of coding of attended objects in V1/LOC. Further, we hypothesise that TMS to the rIPS during low load may not influence object coding across the MD network, given that the network is not actively engaged when perceptual difficulty is low (Woolgar et al., 2015).

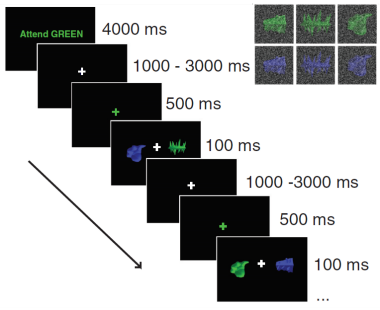

Figure 1. Experiment paradigm: participants will be cued to attend to either blue or green stimuli at the start of each block, and asked to identify the attended object ('cubie', 'smoothie', or 'spikie') by pressing one of three response keys. They will learn and practice three different response-mappings before the scanning session. At the start of a trial, a white fixation will be shown for a variable interval of 1-3 s, after which a 500 ms 'ready cue' will be presented in the cued target colour. During the stimulus display, one green and one blue object will be presented on either side of a white fixation cross for 100 ms. On each trial, the object in the relevant colour is the target ('attended object') and the object in the other colour should be ignored ('distractor'). The configuration of green and blue objects will vary randomly from trial to trial, making the spatial location of the target unpredictable. Although easily visible stimuli are presented here, the perceptual demand of the task will be increased by superimposing Gaussian noise in front of the stimuli (as can be seen on the top right).

Separating Episodic and Semantic Memories

Unique Code: PP001161

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Topic: Cognition and behaviour

Introduction.
The distinction between episodic and semantic memory is supported by a large corpus of neuropsychological studies. However, neuroimaging data show considerable overlap between brain regions that are involved in semantic and episodic processing. While this overlap might indicate similar processing, it might also result from confounded task designs or sub-optimal fMRI protocol. In this planned fMRI study, we aim to distinguish retrieval of semantic and episodic memories using closely matched tasks, in which episodic and semantic processes are minimally confounded.

Methods.
Stimuli will be 240 pictures of logos, paired with the names of the company/product they represent and with an unrelated name. Participants will complete two paired-associate cued-recall tasks, as well as a control task (letter identification). In the episodic task, they will study unrelated logo-name pairs, and will then view logos and recall the associated studied name. In the semantic task, a similar recall procedure will ensue, but participants will retrieve the associated name from their prior knowledge. Furthermore, to examine content effects via recall-related activity pattern, the cued-recall phase will be followed by an evaluation phase, in which the name is presented and information about the episodically/semantically associated item is retrieved.

Approach for statistical analysis.
Bayesian linear mixed-models (BRMS) will be used to estimate differential processing and content effects of episodic and semantic memories. We will contrast activation for recall success vs. failure trials (the “recall success” effect) to estimate differential processing. We will further contrast the similarity between trials referring to the same episodic/semantic instant and trials referring to different instances to estimate content effects.

Predictions.
We predict that some areas will show a greater recall success effect and a greater content effect in the semantic vs. episodic task (e.g. anterior temporal lobe), while others will show the opposite pattern (e.g., hippocampus). Taken together, we expect the results to indicate that semantic and episodic memories are intertwined but distinct.

The development of boundary-based spatial memory in 8- to 15-year-old children

Unique Code: PP001163

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Topic: Cognition and behaviour

Efficient navigation through the environment is crucial to our everyday life. To achieve this, humans and other animals form cognitive maps of their environment. Place cells and grid cells in the hippocampus and entorhinal cortex, respectively, are considered to be the neural substrates of these cognitive maps. The hippocampal-entorhinal system is thought to particularly support boundary-based spatial representations. In rats, place cells and grid cells continue to develop throughout the first weeks of life. Consistently, human hippocampal structure and function keeps developing throughout adolescence. However, little is known about the development of boundary-based spatial memory. It is not fully developed at age 10 and it is unknown how the development continues beyond this age. In contrast, learning positions relative to local landmarks, which recruits the striatum, has been observed to reach adult-like levels by 6 years of age. To investigate the developmental trajectory of boundary-based relative to landmark-based spatial memory, we will conduct an online experiment in which children between the ages of 8 and 15 years will learn positions of 4 objects in a circular virtual enclosure with an intra-maze landmark and distal cues. Later, participants will indicate remembered locations of the hidden objects over multiple trials. Between blocks, the location of the landmark will be changed. Participants will learn that two objects are tethered to the landmark, so that their correct locations shift correspondingly, whereas correct positions for the boundary-based objects remain constant across blocks. We predict that the precision of children's object position memory will improve with age when learning positions relative to environmental boundaries. In contrast, we expect that landmark-based positional memory will stay relatively constant. Using mixed effects modelling, we will test for an interaction of the fixed effects of participant age and object type (tethered to boundary or landmark) on object position memory. This study will fill a gap in our knowledge about the development of human spatial memory and will improve our understanding of cognitive development during adolescence.

When are naturalistic events encoded to memory?

Unique Code: PP001172

Authors: Kevin Campion - University of Cambridge MRC Cognition and Brain Sciences Unit, Richard N. Henson - University of Cambridge MRC Cognition and Brain Sciences Unit, Aya Ben-Yakov - University of Cambridge MRC Cognition and Brain Sciences Unit

Topic: Cognition and behaviour

Naturalistic stimuli have provided an avenue to address a fundamental question about episodic memory – when are events encoded? Importantly, while viewing film clips, hippocampal activity increases at event boundaries [1, 2] and these increases have been associated with better memory for the preceding event [3].

Studies of naturalistic hippocampal event encoding have largely focused on coarse-grained events. However, an important characteristic of events identified in behavioural studies of event segmentation is that they form a complex partonomic hierarchy [4]. For example, the coarse-grained event “dinner” may comprise the sub-events “cooking” and “consuming”, which in turn may comprise fine-grained events such as “chopping carrots”, “drinking water” etc. The level in this hierarchy at which hippocampal encoding occurs remains an open question; are fine-grained events encoded as they occur, or retroactively at higher-level event boundaries?

To address this question, we will use functional magnetic resonance imaging (fMRI) to measure brain activity while participants view an extended video (~40 mins). This video will depict a series of events, created using The Sims 4 life simulation video game. Events will be bounded by a boundary from one of four levels, which are, ordered from finest to coarsest: an action change (n = 200), a small spatiotemporal change (n = 100), a large spatiotemporal change (n = 50),

and a character change (n = 25). Following scanning, participants' recall for all actions will be tested using pictures of the characters as cues.

To test the link between subsequent memory and hippocampal activity at boundaries, we will create a generalized linear mixed model with action recall as the dependent variable and univariate hippocampal activity at the four boundary levels as independent variables. Evaluating the variance in recall explained by each variable will allow us to determine the boundary level at which fine-grained events are encoded.

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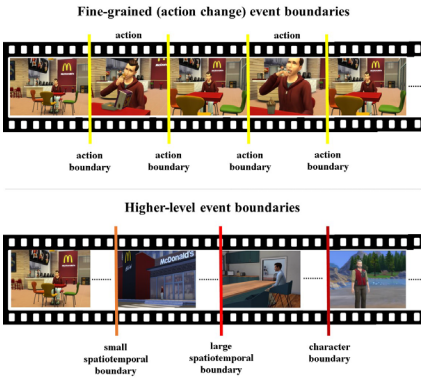

Investigation of interactions between medial prefrontal cortex and hippocampus in a rat model of Fragile X Syndrome

Unique Code: PP001177

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Topic: Cognition and behaviour

Fragile X Syndrome (FXS) is one of the most common inherited forms of intellectual disability and autism spectrum disorder. Mouse and rat models of FXS have been produced through knockout of the Fmr1 gene, and numerous behavioural and physiological deficits have been observed in these models. Previous data from the lab has shown that the rat model fails to show memory for object-place-context associations in a spontaneous object exploration recognition memory task, which is reliant on intact connections between medial prefrontal cortex (mPFC) and hippocampus. More generally, interactions between these areas are important for cognitive flexibility and adaptation to novelty, which has been shown to be affected in FXS patients. This study aims to investigate whether differences in

functional connectivity between mPFC and hippocampus underlie these deficits. This will be done by implanting tetrodes into the mPFC and hippocampus of adult male Fmr1 KO and littermate control (WT) rats, and recording single units and local field potentials (LFP) from both areas simultaneously, while the animals freely explore novel and familiar environments and object configurations. Interactions between the networks will be assessed by looking at changes in LFP power and coherence, and phase-locking of individual neurons, at specific phases of the tasks, and across sessions and days to compare experience-dependent changes between the two genotypes. The general statistical design is a between-subjects model, with session and day as repeated measures. To analyse single unit data, where multiple cells are recorded from each animal, a generalised linear mixed effects model design will be used to take into account random variability between individual subjects in each group. Differences in mPFC-hippocampus network interactions between the genotypes would show altered processing in an important memory circuit, which could underlie cognitive deficits seen in FXS patients.

Diurnal rhythms of impulsivity: Are there times of the day when we are more impulsive, and how do our sleep patterns impact this?

Unique Code: PP001178

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Topic: Cognition and behaviour

Introduction

Many aspects of human cognition vary throughout the day. 'Time of day' effects may also interact with sleep patterns, with poor sleep leading to stronger diurnal expression of cognition. However, despite clear links between insufficient sleep and impaired response inhibition, it is unclear whether individuals' levels of impulsivity vary throughout the day. This study will determine whether there are certain times in the day that individuals tend to be more impulsive; whether such effects are impacted by their sleep patterns; and whether sleep patterns are associated with different levels of impulsivity. Importantly, we will use this data to inform the methodology of a subsequent neuroimaging study, using fMRI, investigating changes in neural activity when participants' sleep patterns are altered.

Methods

Participants will be healthy students reporting no mental health condition, ADHD, or sleep problems; and no psychoactive medications. To index how motor impulsivity changes during the day, participants will complete a Stop Signal Task (SST), at five timepoints (9am, 12noon, 3pm, 6pm and 9pm). Session order will be counterbalanced to mitigate potential practise effects. Response inhibition will be indexed by Stop Signal Reaction Time (SSRT). Participants will keep a sleep diary for 7 days, to determine how sleep patterns impact diurnal SST performance. Questionnaire measures of sleep quality, chronotype, wellbeing and trait impulsivity will be taken.

Approach for statistical analysis

To compare SSRT at the five timepoints, we will use a 5x1 repeated measures ANOVA. If significant, we will explore the direction with post-hoc repeated measures T-tests. If the ANOVA is non-significant, but we observe indicative difference between two timepoints visually (non-overlapping 95% CI error bars) we will compare these with repeated measures T-tests. To see how sleep patterns influence diurnal SSRT, we will calculate a difference score (SSRTtime1– SSRTtime2) to enter as a multiple regression dependent variable, with sleep duration, quality and chronotype as independent

variables. Finally, we will explore relationships between our individual difference measures using a correlation matrix. Statistics will be performed in R, using BFs as well as p values.

How do we feel others' pain? Are there individual differences?

Unique Code: PP001189

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Topic: Cognition and behaviour

Vicarious pain (Empathy for pain) means having pain-like experiences when seeing others in pain, and its relationship with physical pain is not clear. Some studies suggest physical pain and vicarious pain share common representations, while others proved their brain patterns are distinct. However, a middle ground is possible where some people have shared representations and others do not. Based on a vicarious pain questionnaire (Grice-Jackson et al., 2017), we found three types of people when seeing others in pain: Affective/general (AG) group tend to express affective and non-localized pain; Sensory/localizer (SL) group tend to report sensory and localized pain; Non-responders do not experience any vicarious pain. So, we aim to explore whether physical pain and vicarious pain share common representations while considering the individual differences of vicarious pain.

Our study consists of two parts, including 60 subjects (20 from each group). One is the pre-test, which is used to measure the pain threshold of the subjects. One is a formal functional magnetic resonance imaging scanning (fMRI) experiment, which includes two tasks. One is cue-based physical/ vicarious pain paradigm. This is a 2(self/other) X 2(hand/foot) X 3 (no/low/high pain level) within-subject quick event design. Participants either be shocked themselves or watch the researcher being shocked, depending on the direction of the arrow(cue). Another is an image-based vicarious pain paradigm. It is a 2 (foot/Hand) x2 (no pain/Pain) design. Participants will be presented with a series of pictures showing pain or no pain.

Firstly, univariate analysis is used to see what brain regions are involved in each condition (contrasting pain v. no-pain in each group).Secondly, we will use Multivariate pattern analysis to make prediction for different condition among different groups. To be specific, each subject's data will be divided into a training set and a test set. We will use the training set to train a classifier to detect physical pain or vicarious pain, then we use 5-fold cross-validation to evaluate it.

Can psychedelic (±)-DOI have long-term effects on cognitive flexibility in a two-step decision-making task for mice?

Unique Code: PP001203

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Topic: Cognition and behaviour

Psychedelics rapidly promote neural plasticity beyond the acute intoxication phase, an ability thought to underlie their long-lasting positive effects on behaviour. We hypothesize that the resulting rich synaptic landscape would lead to observable brain structural changes and favour the encoding of new information in the long term. Theoretically,

inducing a more efficient and flexible cognition could counteract persistent maladaptive habits which underlie many neuropsychiatric disorders.

Methods: We aim to test if the psychedelic (±)-DOI improves cognitive flexibility in a mouse two-step decision-making task. Water-restricted young adult C57 mice will learn a fixed sequence of two choices leading to a reward whose probability changes over time, requiring mice to continuously search for the highest-reward choice. After training, animals will receive one injection of 2mg/kg (±)-DOI or saline (n=13/group) in an observation cage. For the next 2 weeks, performance on the two-step task will be monitored after reversals in reward probabilities and in the sequence of the two choices. We predict that (±)-DOI will improve task performance by increasing the speed and/or accuracy of relearning following reversals. All mice will undergo three types of ex vivo MRI – T2 weighted structural scan, and a multi-shell diffusion and quantitative susceptibility sequence.

Analysis: Learning accuracy will be quantified by the percentage of correct choices at the end of reward reversal blocks, while the speed of relearning will be measured by the percentage of correct choices following reversals. Unpaired t-tests will compare the drug and control group performance and acute drug responses (head twitches, ear scratches) will be correlated to any changes in cognitive performance. Trial-to-trial learning will be assessed by logistic regression models of stay probabilities as functions of trial outcome (rewarded or not), choice sequence (common/rare), and their interaction. Fitting reinforcement learning models will show if the drug affected what behavioural strategies animals use to solve the task. Analysis of MRI datasets (morphometry, diffusion tensors, quantitative susceptibility mapping) will quantify changes in both white and grey matter across the whole brain.

HOW SEMANTIC PREDICTIONS MODULATE MEMORY ENCODING IN SENTENCES

Unique Code: PP001206

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Topic: Cognition and behaviour

1. Introduction:

Events that are congruent with expectations (or “schemas”) are better remembered than unrelated events. Yet, events that conflict with schemas can also be better remembered, resulting in memory being a “U-shaped” function of schema (in)congruency. According to the Schema-Linked Interactions between Medial prefrontal and Medial temporal regions (SLIMM) framework (Van Kesteren, et al., 2012), this U-shape reflects the operation of distinct memory systems, with the medial prefontal cortex (mPFC) supporting the congruency advantage and the medial temporal lobes (MTL) supporting the incongruency advantage. Moreover, SLIMM predicts that the types of memory differ, with the MTL system encoding a snapshot of incongruent events that can include incidental “context” information; whereas the mPFC system discards context information for congruent events. We recently confirmed these predictions using experimentally-trained rules (Greve et al., 2019), and now wish to test them with more naturalistic stimuli, namely sentences.

2. Methods:

Participants study a series of sentences which render upcoming words more or less predictable. At the end of each

sentence is a “critical” noun that is either semantically congruent, unrelated or incongruent with the preceding gist. Each sentence also contains an earlier “contextual” adjective that is incidental to this gist. Memory for critical and context words is then tested using 3 alternative forced choice with semantically-similar lures.

3. Approach for statistical analysis:
SLIMM predicts better memory for congruent and incongruent critical words, relative to unrelated words, but that memory for context words is only better in the incongruent case. Contrary to SLIMM, pilot data suggests better memory only for critical words that are incongruent, and for context words that are congruent. The pilot data will be used to power a preregistered study to confirm whether or not SLIMM’s predictions hold with such stimuli.

4. References:
Greve, A. et al. (2019). Knowledge is power: prior knowledge aids memory for both congruent and incongruent events, but in different ways. Journal of Experimental Psychology: General.

Van Kesteren, M.T.R., et al. (2012). How schema and novelty augment memory formation. Trends in Neurosciences, 35, 211-219

A DWI study investigating the association between structural connectivity of the frontoparietal network with response inhibition difficulties in ADHD

Unique Code: PP001209
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Topic: Cognition and behaviour

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterised by multiple impairments to executive functioning, including to response inhibition. Recently, this impairment has been associated with reduced functional connectivity between the inferior frontal gyrus and the intraparietal cortex, which is negatively scaled with ADHD symptomatology (Kolodny et al., 2020). The current study aims to investigate whether atypical IFG-IPS structural connectivity (SC) underlies response inhibition performance in ADHD, and whether it is associated with symptom severity.

Diffusion Weighted Imaging (DWI) data has been previously collected on a Prisma 3T Siemens MRI scanner as part of Kolodny and colleagues (2018, 2020) study, for both an ADHD and a control group (n=51), using a 2D echo planar imaging sequence: slice thickness = 1.7mm, diffusion gradient directions = 64, TR = 6900 ms, TE = 53 ms. Adult Self-Report Scale (ASRS) and response inhibition performance scores on a Go/NoGo task were also collected.

DWI preprocessing will use the FMRIB Diffusion Toolbox, following the standard outlined by FSL. Using probtrackx, the number of white matter tracts connecting the IFG and IPS in each hemisphere will be estimated, producing values for the number of streamlines connecting the ROIs in each direction, and the total number of connecting streamlines. The following main hypotheses will then be tested:

1. SC between IFG and IPS is reduced in ADHD vs. controls: permutation tests will assess group differences (ADHD vs. Control) in the probtrackx outputs.

2. SC between IFG and IPS is scaled with ADHD symptomatology: Pearson's Rank Correlational Coefficients will be calculated between each of the probtrackx outputs with ASRS total score.

3. SC between IFG and IPS is associated with response inhibition performance: Pearson's Rank Correlational Coefficients will be calculated between each of the probtrackx outputs and the response inhibition performance scores.

Assuming our results support our hypotheses, we will be able to point to an important structural marker for general ADHD symptomatology, and specific response inhibition impairment, thus further establishing the contribution of IFG-IPS circuitry to the manifestation of ADHD.

Histological Phenotyping of the Dp2(10)(10)2Yey mouse model of Cognitive Impairment in Down Syndrome

Unique Code: PP001209

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Topic: Cognition and behaviour

Introduction: Down syndrome (DS) is the most common genetic cause of intellectual disability, arising from trisomy of human chromosome 21 (Hsa21). People with DS demonstrate cognitive impairment in executive function and working memory. Neuroimaging studies suggest that cognitive impairments in DS individuals may arise as a result of global brain morphological changes, reduced regional neural number and densities as well as altered dendritic branching. Our lab, using the Dp(10)2Yey mouse – which has 3 copies of a region of just 37 of the >230 Hsa21 gene orthologues in mouse – reported spatial working memory deficits associated with altered hippocampal neural dynamics. Representations of the external environment are encoded by excitatory pyramidal cells, and the activity of these pyramidal cells are modulated by a diverse population of inhibitory interneurons. Interneuron diversity is largely due to differences in molecular expression profiles. Here, using histological techniques, we will investigate the dorsal hippocampus (dHP) and medial prefrontal cortex (mPFC) for changes in interneuron cell numbers and brain morphology in Dp(10)2Yey mice.

Methods: Perfusion fixed brain tissue from 3-month old male and female Dp(10)2Yey and wild-type control mice will be used. We will investigate cell counts of interneuron populations in cleared coronal brain slices (≤400µm thick) from dHP (n=10+10) and mPFC (n=10+10) – using a modified iDISCO protocol. Brain slices will be imaged on a confocal microscope and cell counts calculated using StereoMate software. Cleared whole brains (n=2+2) will be imaged using a light sheet microscope and analysed using Elastix software to register autofluorescence brain slices to the Allen Brain Atlas to determine global morphological changes in Dp(10)2Yey mice.

Statistical analysis: If the data is normally distributed, Two-Way ANOVA will be used to investigate the interaction between genotype and sex. If a significant interaction is present, then Bonferroni post-hoc analysis will be conducted to

determine simple main effects. If there is no significant interaction between sex and genotype, data will be pooled by genotype and Student's T-test will be performed to investigate statistical differences between genotypes.

The effect of perceptual change and prediction error in the spatial boundary effect on temporal order memory

Unique Code: PP001212

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Topic: Cognition and behaviour

As we experience the world through a continuous stream of sensory input, our brains are constantly trying to predict what comes next. Prediction errors (PE) can result in "event boundaries", which segment our memories for our experiences. Walking into a new room is thought to trigger such a boundary, as evidenced by better temporal order memory for objects within the same room than for objects in different rooms, e.g. in a virtual environment (Horner et al., 2016). However, walking between rooms also typically results in large perceptual changes (PC). We propose an experiment to tease apart the contributions of PE and PC to the formation of event boundaries.

We designed an "M-room" (Panel B) for virtual environments. When traversing such a room, the viewer can only see one half of the room until they reach the middle section. This enables independent manipulation of PE and PC (Panel C): PC can be induced by changing the wall colours between the two halves of the room, and PE can be induced by presenting a cue indicating the colour of the second half, which is then violated.
The first step will be a pilot study to verify that crossing to the second half of the room in the M-room in the absence of PC or PE does not constitute a boundary. To test this, we will examine whether the superior temporal order memory for objects within the same room is similar in M-rooms and the "O-rooms" (Panel A) used in Horner et al. (2016). Participants will encounter objects (total 88) in a series of virtual rooms under the instruction to remember their order.

If M-rooms exhibit the same pattern as O-rooms, we will proceed with the main experiment, using M-rooms to independently manipulate PE and PC. The experiment will be powered based on the pilot. Our key measure will be accuracy in a temporal order memory task. For the pilot, we will compare accuracy between within and across boundary associations for each room type with Bayesian t-tests, while for the main experiment we will run a 2x2 (PE X PC) Bayesian ANOVA to test whether these conditions have additive effects and compare each condition to across room accuracy with Bayesian t-tests.

Horner AJ, Bisby JA, Wang A, Bogus K, Burgess N. The role of spatial boundaries in shaping long-term event representations. Cognition. 2016.

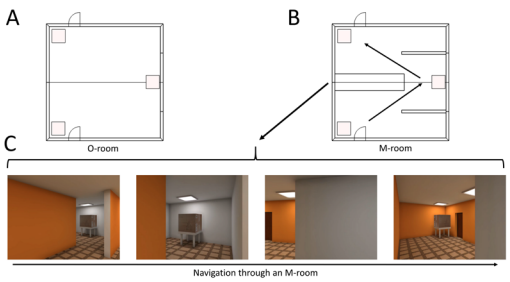

Figure Top left showing the layout of a standard O-room. Top right showing the layout of an M-room with arrows illustrating the navigation path. Screenshots at the bottom show the camera view while navigating through an M-room.

Effects of oxytocin modulation on social fear learning in rats

Unique Code: PP001243

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Topic: Cognition and behaviour

Introduction

Social fear learning occurs when an animal learns to react to a conditioned stimulus by observing another animal's reaction to it, after the first 'demonstrator' animal was fear conditioned. My proposed project aims to elucidate the mechanism behind how animals observe and internalize fear behavior of other animals by focusing on oxytocin modulation in the observer animal.

Methods

A robust olfactory fear conditioning protocol will be set up and responses to the odour will be tested in the original and varied contexts to become context independent. The conditioned "demonstrator" group will then be placed in a context with a rat that was not fear conditioned – the "observer" group, and presented with the odour. The observer rats will be tested independently for odour avoidance after observing the fear-like behavior of the demonstrator.

In order to understand if additional oxytocin signaling enhances social fear learning, the demonstrator rats will be placed in the two-chamber box with observer rats that were just administered oxytocin receptor agonists through an intraperitoneal injection. The observer rats will then be tested with the odour in one compartment and no odour in the other compartment in order to see if enhanced oxytocin levels had an effect on the strength of observer rats learning vicariously. The inverse experiment will be carried out using oxytocin receptors using antagonists, thus taking away oxytocin's role in social fear learning. The results of these experiments will reveal how the presence or absence of oxytocin signaling directly impacts how the observer rats learn from the conditioned rats.

Statistical Analysis

In order to analyse the effects of groups and CS presentation on freezing, repeated measures two factor ANOVAs with post hoc Sidak correction tests will be performed. Avoidance behaviour across chambers will be analysed by 1-way ANOVA and simple between groups comparisons using independent samples two-tailed t-tests. Statistical significance taken to be at $P<0.05$.

Understanding the mechanisms underlying altered neural dynamics and GABA over-inhibition in the Dp1Tyb mouse model of Down Syndrome

Unique Code: PP001250

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Topic: Cognition and behaviour

Introduction
Down syndrome (DS), which results from trisomy of human chromosome 21 (Hsa21), is the most common genetic cause of intellectual disability. Although DS arises from increased dosage of Hsa21 genes, the specific mechanisms underlying cognitive dysfunction remain unknown.

Previous results from our laboratory suggested that the cognitive impairment presented by the Dp1Tyb mouse model of DS, which has 3 copies of a region of 148 coding genes with orthologues on Hsa21, might be caused by altered hippocampal-prefrontal cortex neural dynamics and excessive GABA inhibition.

Consequently, we are now trying to elucidate the molecular and cellular mechanisms responsible for the cognitive impairment in these mice paying special attention to the potential involvement of defective GABA signalling in neural connectivity and/or cognitive function.

To do so, we will start by checking if there is an increase in the number of hippocampal interneurons in Dp1Tyb mice.

Methods
In order to check if the excessive hippocampal GABA inhibition observed in 3-month old Dp1Tyb mice is caused by an alteration in the number of interneurons, we are going to use a histological approach. Specifically, we will use a modified iDISCO protocol to clear ≤400µm thick coronal sections of the brains of male and female Dp1Tyb and wild-type littermate control mice (n=5 males+5 females per group) sacrificed at 3 months of age by transcardial perfusion.

Brain slices will be stained with fluorescently-labelled antibodies against parvalbumin, somatostatin, calretinin, neuropeptide Y, neuronal nitric oxide synthase, vasoactive intestinal peptide and cholecystokinin, markers of the main interneuron populations in the hippocampus. Slices will be then imaged using confocal microscopy and absolute cell counts in the hippocampus will be calculated using the StereoMate software.

Approach for statistical analysis
A Two-way ANOVA will be use to check if there is interaction between genotype and sex. If there is such an interaction, a Bonferroni post-hoc test will be then conducted to determine simple main effects.

Brain connectivity and patient reported outcomes in people with HIV with symptoms of insomnia switching integrase inhibitor-based ART

Unique Code: PP001259
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Topic: Cognition and behaviour

Antiretroviral toxicity is a common cause for therapy modification with around a quarter of individuals on first-line combination antiretroviral therapy (cART) changing treatment due to the onset of toxicity, including CNS toxicity, manifested clinically with neuropsychiatric symptoms. Emerging data from cohort studies suggest higher risk of CNS adverse events for dolutegravir-containing regimens compared to other integrase inhibitors, with insomnia being the

most common symptom reported. fMRI has shown promise as a method to determine differences in cerebral function parameters between antiretroviral agents and combinations. Recently, we demonstrated changes in brain connectivity in virologically suppressed people with HIV (PWH) with no neuropsychiatric symptoms, switching from raltegravir to dolutegravir containing ART, measured via fMRI in several brain networks using a behavioral stop signal reaction times (SSRT) task that evaluates inhibitory control, the process of being able to suppress interfering information to focus on complex tasks, an important pre-requisite for executive function. Furthermore, poor inhibitory control has been associated with sleep difficulties and cognitive impairment in HIV negative individuals. Different antiretroviral agents and combinations may have differing effects on cerebral function which are well recognised between the different non-nucleoside-reverse-transcriptase-inhibitors and protease inhibitors. Less data exists for differences in cerebral function parameters between the integrase inhibitors and no data exists comparing cerebral function parameters using fMRI in PWH with insomnia switching from dolutegravir to bictegravir (a recently approved integrase inhibitor ART medication associated with less CNS adverse events). In this study we aim to investigate changes in brain fMRI parameters (baseline and 120 days post-switch) in PWH with symptoms of insomnia switching from dolutegravir to bictegravir (23 switching; 23 remaining on previous regimen) with the interaction of interest being switch status x timepoint. We hypothesise that switching will be associated with changes in brain activity measured via whole brain fMRI (thresholded at $p<0.05$ cluster-wise FWE), and in fronto-striatal connectivity.

Development of cortical head-direction coding in wild-type and Fmr1 knockout rats

Unique Code: PP001272

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Topic: Cognition and behaviour

Fragile X Syndrome is one of the most common monogenic causes of autism. Fmr1-KO rodents show disrupted cortical information processing in early postnatal development, but how such circuit abnormalities affect development of neural representations is unclear due to the limited behavioural repertoire in neonates. To overcome this, we focused on the head-direction (HD) system, the brain's 'compass', as a model for cortical information processing. The HD system is a thalamocortical circuit: the HD signal is relayed to the cortex via the anterior thalamus. Together, the population of HD neurons encodes a one-dimensional circular variable (current direction in allocentric space) and shows rigid co-activity patterns that are preserved even in absence of consciousness. Thus, the aim of the project is to characterize the development of the HD system in neonatal Fmr1-KO rats focusing on the first cortical stage of the circuit - the postsubiculum (PoSub).

We will record assemblies of HD cells in the PoSub of Fmr1-KO rats and littermate controls from the second postnatal week until early adolescence using high-density silicon probes. Recordings will be performed either chronically in awake animals, or acutely under urethane anesthesia.

We will compare activity patterns of PoSub cells across different developmental stages. Population recordings will enable us to look not only at spatial correlates of individual cells but also at temporal co-activity relationships on a population level. This in turn will allow for characterisation of functional deficits in cortical development in neonates

that do not yet actively explore the environment. Approaches will also include extraction of relative HD cell receptive fields from population activity using manifold-based dimensionality reduction techniques. Importantly, such techniques allow for reconstruction of network topology in absence of behaviour (Chaudhuri et al, 2019, Nat Neurosci. 22:1512-1520).

We have successfully recorded populations of up to 30 HD cells in P23-28 freely-moving rats. Preliminary data indicate that Fmr1-KO rats have intact HD tuning in superficial layers of PoSub but impaired HD tuning in deep layers. This is in line with reported deficits in cortical processing in Fmr1-KO rodents in vitro.

Optogenetic Locus Coeruleus activation of tyrosine-hydroxylase-expressing neurons enhances everyday memory in rats

Unique Code: PP001306

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Topic: Cognition and behaviour

Retention of episodic-like memory is enhanced when something novel happens shortly before or after encoding (Wang et al., PNAS,2010). Such memory selectivity appears to be sensitive to blockade of hippocampal dopamine receptors. The putative hippocampal dopamine consolidation signal was hypothesised to arise via a hippocampal ventral tegmental area loop (Lisman and Grace, Neuron, 2005), but recent optogenetic studies have pointed to the possibility of locus coeruleus (LC) co-release of dopamine in mice (Takeuchi et al., Nature,2016; Kempadoo et al., PNAS,2016). The initial aim of this study was to examine the generality of this finding in tyrosine hydroxylase-cre rats.

We have optimised an appetitive everyday memory task which promotes allocentric memory representations of 'episodic-like' spatial memory through use of a stable 'home-base' (Broadbent et al., EJN,2020). The locations of available hidden reward vary daily but, once learned, the rats perform well by remembering the event location for a few hours but forgetting overnight. Brief optogenetic stimulation of LC (25Hz, 5 min) scheduled 45 min before or 30 min after daily memory encoding successfully transformed such transient memories into more lasting representations (24 h). Consistent with the concept of synaptic tagging and capture, we are presently examining the pharmacological basis of this phenomenon.

A key design feature of the everyday memory paradigm is that each animal serves as its own control, with various test conditions repeated across days using a counterbalanced design. This within-subject design minimises the number of animals required to achieve statistical power and enables the use of within-subject estimates for performance variability. Statistical analyses will be performed using SPSS. Data sets will be tested for normality using the D'Agostino-Pearson test. When normality was met, statistical significance was determined using the appropriate parametric analysis such as repeated-measures ANOVA.

Our results are part of a program of research exploring the automatic nature of episodic-like memory encoding and the selectivity of its retention. The notion is that the retention of glutamatergic memory representations is modulated by catecholamines in the HPC.

Association between stress levels with fixation and high carbohydrates food selection, measured by Eyetracking

Unique Code: PP001370

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Topic: Cognition and behaviour

INTRODUCTION Stress response, triggered by real or potential threats, results in homeostasis alteration and fight or fly behaviors. When stress becomes chronic it turns into a maladaptive condition, stress could induce sustained high cortisol blood levels and insulin resistance contributing to abdominal-visceral obesity development and could trigger food consumption in the absence of hunger and low satiety levels after eating. Studies aimed at researching alimentary stimuli effects on reward system have found a dopamine mediated activation of amygdala, striatum, anterior cingulate cortex, orbitofrontal cortex and hippocampus; this phenomena could explain why in the context of high stress levels people are prone to select high carbohydrates/ fat content food; due to their rewarding effects. Some studies have documented the relationship between stress and obesity, however more evidence is needed to support the design of behavioral interventions for obesity and overweight. METHODS working hypothesis of the present study is the possitive association between high stress levels and fixation related with high carbohydrates food, measured with eyetracking. 20 participants will be recruited and blinded for the principal objective of the study. PSS10 validated stress test will be used to assess stress; taking >25 as threshold of high stress levels. Pupil labs w120 e220b will be used to measure fixations, fixation times and saccadic movements. Participants will be exposed to random images (food, objects, places). Each visual field will have an A image and a B image; participants will be asked to select their preferred image (A or B). Average fixation time and number of fixations for each area of interest will be measured. STATISTICAL ANALYSIS: Includes descriptive analysis of categorical variables with relative and absolute frequencies, as well as Bivariate ANOVA analysis of stress levels and food selection (high and low carbohydrates content); along with mixed effects linear regression (Alfa 0,05) on eyetracking data, aimed to evaluate the association between fixation time and high carbohydrates food selection.

KEY WORDS: Eye-Tracking Technology; Psychological Distress; Obesity; Abdominal, Obesity.

Investigating Perceptual Closure Differences Between Dyslexics and Controls when Identifying Fragmented Words and Objects

Unique Code: PP001383

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Topic: Cognition and behaviour

The magnocellular theory of dyslexia suggests that dyslexics have reduced contrast and motion sensitivity at low spatial frequencies and illuminative levels (Stein & Walsh, 1997). This is attributed to a difference in the structure of the lateral geniculate nucleus in the magnocellular pathway of the visual system. Impaired perceptual closure, a processing deficit in the ability to identify fragmented visual stimuli, is attributed to impairments in this pathway. Doniger et al. (2002) identified an ERP for closure negativity differences between schizophrenics and controls at posterior electrode sites,

indicating impaired perceptual closure for schizophrenics. The present study aims to identify whether the same differences exist in those with and without dyslexia whilst also investigating whether the effect persists between fragmented abstract and concrete words, as well as objects. A partial replication of Doniger et al. (2002), with the addition of words as stimuli, will be run using a 32-channel EEG recording system. Participants will be presented with images of words and objects with progressively less fragmentation until the stimulus is identifiable. ERPs for abstract words, concrete words and objects at the point of identification and the 3 iterations prior to this will be extracted from the data. A four-way mixed ANOVA will be conducted to investigate whether significant differences exist between individuals with and without dyslexia on the mean ERP amplitudes based on the point of identification and the 3 iterations beforehand. Type of stimulus (word or object) and word condition (abstract or concrete) will also be investigated. By identifying the electrophysiological basis of perceptual closure deficits in those with dyslexia, this study may establish a new endophenotype. Further research could utilise this endophenotype to investigate closure negativity as a classifier for dyslexia.

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Stein, J. & Walsh, V. (1997). To see but not to read; the magnocellular theory of dyslexia. Trends in Neurosciences, 20(4), 147-152.

Effects of APOE genotype on brain activity during movie watching

Unique Code: PP001384
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Topic: Cognition and behaviour

Introduction: APOE e4 is the largest genetic risk factor for late-onset Alzheimer's disease. It has been associated with poorer episodic memory in older age and higher default mode network (DMN) connectivity compared to e4 non-carriers. More broadly, during movie watching, the DMN had been shown to respond to narrative shifts (event boundaries). If e4 carriers show differences in DMN connectivity, a network responsive to event boundaries, this leads to the question of whether APOE e4 carriers display unusual patterns of activity around event boundaries compared to non-carriers.

Methods: This study will use data from the Cam-CAN dataset (https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/) – a group of around 600 APOE genotyped participants representing the adult lifespan. We will examine whether there are genotype differences in boundary-evoked responses to a short film. Using a pre-defined event segmentation of this film (see Ben-Yakov & Henson, 2018), we will test for differences in hippocampal responses to event boundaries, and differences in DMN functional connectivity around boundaries. Finally, we will also consider whether there is an age-dependent effect of APOE genotype on event boundary processing.

Approach for Statistical Analysis: Data will be pre-processed using a pipeline developed by Geerligs, Cam-CAN & Campbell (2018). We will select ROIs from the DMN network and the hippocampus. A GLM will be fitted with event boundaries as a regressor to quantify boundary-evoked activity in each ROI. A PPI will be used to quantify changes in functional connectivity between DMN regions around event boundaries. The results of these analyses will be submitted to a mixed-effects model with planned contrasts to compare differences between APOE genotype and age.

Neural mechanisms of Bayesian optimisation of inhibitory control across the adult lifespan

Unique Code: PP001385

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Topic: Cognition and behaviour

Introduction

Inhibitory control enables rapid behavioural adjustments in light of dynamic task demands. It is a crucial executive function that determines successful function across the lifespan. The locus coeruleus (LC) noradrenaline system is critical for inhibitory control. It modulates responses by signalling unexpected state changes, that reset internal models.

Inhibitory control can be quantified using the stop signal paradigm - a reaction time (RT) task that is occasionally interrupted by a stop signal, requiring the response to be inhibited. Task performance can be summarised with the mean stop signal RT, but this does not directly speak to the trial-wise neurocomputational dynamics underlying inhibitory control. The link between the LC and trial-wise activity in the fronto-striatal 'stopping network' remains unclear.

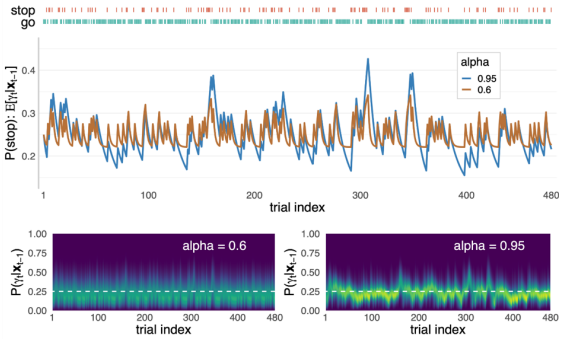
In this study, we will combine Bayesian modelling of sequential learning with functional imaging during a stop signal task and structural imaging of the LC. We will test the hypothesis that individuals with reduced LC integrity show weaker neural responses associated with trial-wise stop signal predictions.

Methods

We will study a representative sample of healthy adults (N=123) from a population-based lifespan cohort (Cam-CAN; Shafto et al., 2014, BMC Neurol), who performed a stop signal task during functional magnetic resonance imaging (fMRI). We will use the Dynamic Belief Model (DBM; Ide et al., 2013, JoN) to infer the participants' trial-wise predicted probability of encountering a stop signal. We will estimate LC integrity from magnetisation transfer imaging, with atlas-based segmentation for LC localisation and signal quantification (Ye et al., 2021, NeuroImage).

Approach for statistical analysis

Hierarchical Bayesian model fitting will optimise the DBM stop signal predictions with respect to the participants' RT data. Specifically, the log prior odds of not encountering a stop signal will serve as the starting point of evidence accumulation towards a go response threshold. The optimised stop signal predictions will then be used as parametric modulators in a general linear model of the fMRI data. Post-hoc interaction analyses will be conducted to assess the moderation of LC integrity on trial-wise activation.



Identifying the network for working memory protection from distractors: TMS-fMRI study

Unique Code: PP001387

Authors: Olga Leticevscaia - School of Psychology University of Reading

Topic: Cognition and behaviour

Working memory (WM) is the ability to hold and manipulate information in mind and is essential for complex cognition. Yet, irrelevant information often disrupts WM, resulting in memory distortion or even forgetting. How the brain protects memories from distracting information is an ongoing debate. In the present study, we aim to contribute to this debate by investigating causally, using transcranial magnetic stimulation during functional magnetic resonance imaging (concurrent TMS-fMRI), the mechanism by which a network of brain regions protects WM contents. Concurrent TMS-fMRI involves application of TMS to a targeted brain region, in this case, dorsolateral prefrontal cortex (dlPFC), to perturb the blood oxygen level-dependent (BOLD) response not only in the targeted region, but also in remote, functionally connected brain regions. This will permit causal inferences to be made on the role of the dlPFC during WM under distraction, as well as the evoked network. During fMRI scanning, participants will perform a visual continuous reproduction task and a short train of TMS will be applied on each trial over right dlPFC. TMS will be time-locked to the middle of the retention period, at the point when visual distractors could appear. We will have a separate scanning session, in which the same task will be performed, with TMS given over a non-WM control site (S1). The data from this session will be used to identify the memory protection network. We will first identify nodes of the network by using whole-brain univariate analysis; subject-level data will be fitted with a general linear model with epoch regressors for each distractor condition. Nodes will be placed at activation peaks defined by the effect of distraction (t-test, $p<0.05$). Then, we will use dynamic causal modelling analysis to identify the effective connectivity between these nodes. To show how the memory protection network re-organises itself when activity in the prefrontal cortex is perturbed, we will perform the same analysis of the data from the session with the TMS applied over dlPFC and compare visualizations of two networks. It will provide us with unique insights for understanding the short-term memory disorders that involve e.g., frontal lobe atrophy, such as frontal or frontotemporal dementia.

Computational and theoretical neuroscience

Unveiling the neural networks underlying the combination-sensitivity property in the HVC neurons of songbirds

Unique Code: PP001361

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Topic: Computational and theoretical neuroscience

Introduction:
A wide range of behavioural experiments in humans and animals show that a common strategy for signal identification and localization is sensitivity to two or more spectral or temporal components of the signal. This feature is known as combination sensitivity and has been extensively studied in echolocating bats, frogs and songbirds. In songbirds, the HVC (used as a proper name) nucleus is a cortical-like area responsible for the bird's singing as well as learning of his song. Neurons in the HVC are sensitive to the temporal structure of the bird's own song and are capable of integrating auditory information over several hundred milliseconds. The HVC is the hub of many response-specific cells, particularly combination-sensitive neurons. These neurons respond in a facilitatory or inhibitory manner to patterns of distinct elements in an auditory signal occurring in a precise temporal order. In this work, we will develop mathematical models for the different classes of HVC neurons and connect them in several networks to unveil the intrinsic and synaptic mechanisms that orchestrate the combination sensitivity properties allowing this unique auditory stimuli temporal processing.

Methods:
e are developing conductance-based neural network models connecting the three classes of neurons via different network architecture patterns with the aim to replicate their in vivo firing patterns observed when various auditory stimuli are presented. The model neurons in each class are designed to express pharmacologically identified ionic currents (Daou et al 2013) and the neurons are connected via pharmacologically identified synaptic currents (Mooney and Prather 2005), rendering our network biologically plausible. Simulations of these model neurons are being performed using custom built MATLAB (MathWorks) code. Our goal is to explore different possible realistic scenarios in which the different types of HVC neurons can interact to produce this behavior.

Statistical Analysis:
The work conducted here is purely theoretical at this point. It is based on deciphering the connections between the neurons using mathematical modeling and does not include any group comparisons or numerical outcomes. Up till this point, no statistical tests can be applied to our project.

Modelling the effects of Deep Brain Stimulation of the Globus Pallidus Interna on Reinforcement Learning

Unique Code: PP001365
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Topic: Computational and theoretical neuroscience

A range of evidence suggests that in the basal ganglia, various neurotransmitters and nuclei play roles akin to Reinforcement Learning (RL) algorithm parameters. RL is a machine learning paradigm that can be conceptualised as the interaction between an agent in a state (st), which makes an action (at) at time 't' and receives a reward (rt) from the environment. The agent utilises exploration and exploitation tactics to develop a map from prior state to subsequent action which maximises cumulative reward. Reward predictions errors (RPEs) allow the RL agent to evaluate whether a response was "good" or "bad". This presents a scenario whereby the basal ganglia receive dopaminergic RPEs from the mesencephalon, which are processed in the basal ganglia and broadcast to thalamocortical loops, resulting in stimulus-response learning.

We hypothesise that stimulation of the Globus Pallidus interna (GPi) will impact the RL step-size parameter 'α'. α encodes how influential rt is upon at+1, at+2... This hypothesis builds upon studies in non-human primates where decision times and stimulus-response learning to novel reward contingencies were impaired by pharmacological ablation of the GPi (Piron et al., 2016).

Twenty-Five patients with focal and segmental primary dystonia with chronically implanted bilateral GPi DBS electrodes will perform a 2-armed bandit task. This task requires them to select from two abstract images, with an underlying reward probability of 80% or 20%. After 60 trials, the reward probabilities are reversed. This task was performed with DBS on and DBS off in a randomised order. For each trial, the patient's reaction time, image selection and reward received is recorded. We plan to fit this data to five hierarchical Bayesian models using the HDDM python package (Wiecki et al., 2013; Pedersen and Frank, 2020). These models are a hierarchical drift diffusion model (HDDM), two Reinforcement Learning DDM models (RL-DDM), and two RL-softmax models.

We plan to validate each model by examining the posterior distribution, autocorrelation, and Gelman-Rubin statistic, before simulating data with the models and comparing to our observed data. We will select the best model and use it to test our hypothesis directly on the mean posterior probability distributions.

Low-threshold (ID) and calcium-dependent (ISK) potassium currents regulate the firing properties of forebrain-projecting HVCRA neurons in zebra finche

Unique Code: PP001381

Authors: Sally Choker - Biomedical Engineering Program American University of Beirut, Daniel Margoliash - Department of Organismal Biology and Anatomy University of Chicago, Arij Daou - Biomedical Engineering Program American University of Beirut

Topic: Computational and theoretical neuroscience

Introduction

Vocal control and learning are dependent on auditory feedback in both songbirds and humans, rendering songbirds an excellent model to study the neural mechanisms of complex learned behaviour. The telencephalic nucleus HVC within the songbird, analogue to the mammalian pre-motor cortex, produces stereotyped instructions through the motor pathway leading to precise, learned vocalization. The forebrain projecting HVC neurons (known as HVCRA) that projects to the robust nucleus of the arcopallium play a critical role in orchestrating the neural circuitry that guides the bird's learning and song production. Whole-cell current-clamp recordings previously performed on HVCRA neurons within brain slices have shown diversity in their firing activity across birds, ranging from transient to stuttering patterns (Daou & Margoliash, under review). We are now developing a biophysical model that captures the diversity of the HVCRA firing

activity. The model is generating predictions about the ionic currents that HVCRA neurons exhibit which will then be tested and verified in the slice using pharmacological manipulations. The model highlights important roles for the low-threshold potassium current (ID) and the Ca2+-dependent K+ current (ISK) in driving the characteristic neural patterns observed in HVCRA.

Methods
We used a single-compartment conductance-based model of HVCRA neurons to estimate the magnitude of the ionic currents. Manual adjustment of the densities of the ionic conductances and additional parameters was performed to match the membrane potential model trajectories to the biological trace in response to applied step currents. To estimate the goodness of the fit, we adopted a feature-based comparison approach in which intrinsic features of simulated voltage traces and biological traces are compared. The model is then validated by testing the fitted model trace to predictions of different current injections.

Approach for statistical analysis
We developed an error function that computes the error of each electrophysiological feature and then averages them together. For each HVCRA neuron, we will perform paired t tests to compare the average error of the fitted and non-fitted voltage traces across different current injections.

Disorders, treatments and translational neuroscience

Can action observation and/or motor imagery be used to improve computer-based actions in people with Parkinson's?

Unique Code: PP001055
Authors: Camilla Woodrow-Hill - Neuroscience and Experimental Psychology University of Manchester, Ellen Poliakoff - Neuroscience and Experimental Psychology University of Manchester, Emma Gowen - Neuroscience and Experimental Psychology University of Manchester, Stefan Vogt - Psychology Lancaster University, Matthew Sullivan
Topic: Disorders, treatments and translational neuroscience

Introduction:
Parkinson's is a neurodegenerative condition characterised by motor symptoms such as resting tremor, bradykinesia and rigidity. Many people with Parkinson's (PwP) experience difficulty when using a computer (e.g. Cunningham et al., 2012) such as reduced keyboard/mouse speed, difficulty clicking or controlling a mouse and hitting accidental keys when typing. Further, PwP are interested to improve computer-based actions (PUK survey). Computer use is becoming an ever more central part of daily life, particularly due to the 2020 pandemic; hence it is crucial to determine if low cost tools could be developed to facilitate computer use. Growing research has indicated that watching others' actions (action observation; AO) and imagining actions (motor imagery; MI) can be effective tools for facilitating movement in PwP (e.g. Bek et al., 2018). Further, recent studies have suggested that combining the two techniques (AO+MI) could be more powerful in improving movement execution than either one alone (Bek et al., 2019). Therefore, the aim of this study is to determine whether AO+MI can facilitate computer-based actions in PwP, and whether this is more effective than MI alone.

Method:
An online within-subjects study design will be utilised with PwP completing the experiment from home. The experiment

will consist of two sections: 1) typing, and 2) computer mouse use. In 1) PwP will be asked to type a word, and in 2) they must click a target with an on-screen cursor. Using tailored measurements, movement speed, accuracy and motor control will be examined across three different conditions: a) AO+MI, b) MI alone, and c) control. The UPDRS, KVIQ and coin-rotation tasks (CRT) will also be administered as measures of Parkinson's symptoms, motor imagery ability and dexterity respectively.

Approach for statistical analysis:
Multivariate linear mixed models will be used to analyse measures of speed, accuracy and fine motor control across conditions a), b) and c), in both typing (1) and computer mouse tasks (2). Regression analyses will be conducted to investigate whether task improvements on 1) across conditions a), b) and c) predict improvements on 2), as well as whether scores on the UPDRS, KVIQ and CRT predict performance differences across conditions.

Rewiring impaired circuits of micturition control after spinal cord injury

Unique Code: PP001207

Authors: Raquel Oliveira - Institute of Psychiatry, Psychology & Neuroscience King's College London, Martin G. Jones - Institute of Psychiatry, Psychology & Neuroscience Martin G. Jones, Stephen B. McMahon - Institute of Psychiatry, Psychology & Neuroscience King's College London, Elizabeth J. Bradbury - Institute of Psychiatry, Psychology & Neuroscience King's College London

Topic: Disorders, treatments and translational neuroscience

Introduction
Spinal cord injury (SCI) results in an abrupt loss of essential body functions such as movement, sensation and control over the bladder. About 90% of patients develop bladder areflexia followed by neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD), leading to long periods of urinary retention, life-threatening increase in intravesical pressure and urinary incontinence. Treatments are limited and only aimed at managing symptoms. Effective therapies require full comprehension of neurogenic lower urinary tract (LUT) pathophysiology and innovative solutions to re-establish neuronal pathways controlling the micturition system. In my studies I will use Chondroitinase ABC (ChABC) to target extracellular growth inhibitors and promote neuroplasticity within the spinal cord in an attempt to restore micturition circuitry and control over the LUT.

Methods
Rats will be submitted to a spinal cord 180 kdyne contusion lesion at the T9 level or sham surgery (controls) and will receive intraspinal injections of viral vectors encoding ChABC, or control vectors, at the lesion site. Behavioural assessments of locomotion and sensation will be performed weekly post-injury. Cystometries and urethral sphincter EMG recordings will be carried out at acute stages (bladder areflexia) and chronic stages (presence of NDO and DSD) of SCI. Conventional tracers, novel viral vector technologies and tissue clearance will be used to map and visualize entire pathways of LUT innervation, and we will use electrophysiology and in vivo calcium imaging to evaluate re-established neuronal connectivity and function. We hypothesise that lentiviral-ChABC will restore spinal and supraspinal pathways, promoting recovery of motor, sensory and autonomic functions and re-establishing control over the LUT.

Approach for statistical analysis
Longitudinal data will be analysed by two-way ANOVA for cystometry and EMG data and two-way repeated measures ANOVA for behaviour, where baseline performance is a co-variate. Histological data will be analysed by one-way

ANOVA. Sample sizes of n=20/ group were generated using G*Power, using previous data, type 1 error threshold, (α) ≤ 0.05 and power (1 − β) ≥ 0.80.

Funding: International Spinal Research Trust (BBS002).

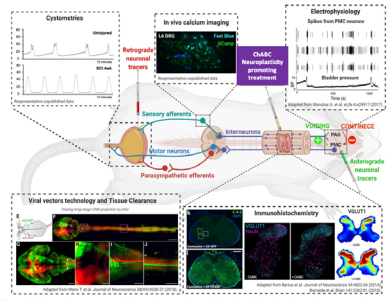

Figure 1: Schematic summary of the project experimental design. Urinary function will be evaluated at acute and chronic stages of contusion SCI and after neuroplasticity-promoting ChABC treatment, by measuring bladder pressure (cystometries) and urethral electromyography (EMG), alongside behavioural assessments of locomotor and sensory function. Afferent and efferent pathways innervating the LUT will be mapped using retrograde and anterograde neuronal tracers, viral vector technology and tissue clearance, to study changes in LUT innervation pathways after SCI and evaluate ChABC-mediated regenerative effects in intraspinal tracts. Mechanisms of sensory and autonomic dysfunction after SCI will be assed using chemogenetic approaches, electrophysiology and calcium imaging techniques. Image created with BioRender.com.

Interneuron distribution affects gamma oscillations in the prefrontal cortex in a mouse model of 22Q11.2 deletion syndrome

Unique Code: PP001221

Authors: Joshua Message - Medical school University of Exeter, Lilya Andrianova - Institute of Neuroscience and Psychology University of Glasgow, Shivali Kohli - Medical School University of Exeter, Gabriella Margetts-Smith - Medical School University of Exeter ,Michel T Craig - Institute of Neuroscience and Psychology University of Glasgow

Topic: Disorders, treatments and translational neuroscience

The extensive connectivity between the prefrontal cortex (PFC) and the rest of the brain is vital for numerous cognitive functions. Disrupted connectivity is associated with schizophrenia (SCZ), a condition difficult to model in animals due to the complex aetiology. Research into rare, highly penetrant mutations such as CNVs (copy number variations) have shed light on understanding the neurobiology of SCZ: around 25% of individuals carrying the 22q11.2 deletion develop SCZ. Here, we have used the Df(16)A+/- mouse model of 22q11.2 deletion syndrome to study circuit changes in a model with translational relevance to SCZ. The synchronous firing of fast-spiking PV interneurons is critical in in coordinating synchronous neural activity that generates gamma frequency oscillations. Gamma oscillations are associated with cognitive processes such as attention and memory. Disrupted PV interneuron function has long been implicated in SCZ, so we hypothesise that PFC in Df(16)A+/- mice will show similar deficits.

In this poster we will characterise the relative frequency, distribution and migration of PV interneurons into the PFC in adult wildtype and Df(16)A+/- mice, using immunohistochemistry. We will record network oscillations using extracellular field recordings from ex vivo slices containing PFC, maintained in interface conditions. We will measure gamma oscillations nested within spontaneous Up states, and also persistent gamma oscillations evoked via bath applied CCh (25 µM) or kainite (100 nM).

We will use multivariate ANOVA analysis to compare the distribution of PV interneurons. Our electrophysiological data will be analysed using custom-written procedures in Igor Pro, using a combination of Fourier and Wavelet analyses. We hypothesise that Df(16)A+/- mice will show disrupted migration of PV interneurons into PFC on both dorsoventral and

mediolateral axes, compared with WT mice. Furthermore, we hypothesise that both spontaneous Up state-nested and drug-evoked persistent gamma oscillations will be disrupted in Df(16)A+/- mice relative to WT.

Identifying neuroinflammatory features of nanoparticles: informing design for clinical applications

Unique Code: PP001255
Authors: Kyle Storey - School of Medicine Keele University
Topic: Disorders, treatments and translational neuroscience

Introduction:
Nanoparticles (NPs) are versatile medical tools with a broad range of applications in the central nervous system (CNS), such as drug delivery and localised thermal tumour ablation. Clinical translation is hindered by a lack of data on the interactions of NPs with CNS-resident immune cells, especially whether particular NP properties are associated with neuroinflammation. This study aims to understand whether the principal CNS immune cells (microglia) show inflammatory responses to specific physicochemical properties of NPs, such as size, surface charge, and surface chemistry.

Methods:
A systematic literature review will identify data on neuroimmune responses to different NP formulations, along with their cellular uptake and toxicity. Properties of NPs associated with biocompatibility and either absence or presence of immune responses will be identified. We will then either commission or purchase NPs with these features. These test NPs will be characterised via dynamic light scattering to assess hydrodynamic size, aggregation and surface charge. Fourier-transform infrared spectroscopy will assess surface chemistry1. Primary rodent microglia cultured within 3D hydrogels will be treated with these NPs (range of doses and timepoints). Secreted inflammatory cytokines and nitric oxide will be assayed (ELISA and Griess). A pro-inflammatory stimulus will be included as a control, with dose-response determined for each assay. Endotoxin is routinely used for this, but we are considering possible alternatives, including intact bacteria.

Statistical Analysis:
Where experimental conditions are sufficiently similar, data from the systematic review will be combined for meta-analysis. Appropriate statistical methods for in vitro experiments are yet to be determined and will be informed by a power analysis, with effect size estimated from our systematic analysis. The presence/magnitude of inflammatory responses (e.g. fold change in secreted IL6, by ELISA) to various NP formulations (at a range of doses and timepoints) will be assessed by one-way ANOVA.

1. Kiefer, J., Grabow, J., Kurland, H. D. & Müller, F. A. Characterization of Nanoparticles by Solvent Infrared Spectroscopy. Anal. Chem. (2015).

Can Piezoceramic Materials Enhance the Regenerative Responses of Neural Stem Cells for Improved Transplantation Procedures?

Unique Code: PP001266

Authors: Imaan Waqar - Life Sciences Keele University, Vladislav Jarkov - Mechanical Engineering Bath University, Hamideh Khanbareh - Mechanical Engineering Bath University, Christopher Adams - Life Sciences Keele University

Topic: Disorders, treatments and translational neuroscience

Introduction

Spinal cord injury affects 40 million people around the globe annually and can lead to reduced mobility and sensation and even paralysis. Currently, there are no regenerative therapies that can repair the injured spinal cord, making this a key clinical goal. One potential repair strategy is the transplantation of neural cells into the site of injury to replace lost tissue and release pro-regenerative molecules. However, lack of control over cell differentiation (into desired cell types) and cell production of pro-regenerative molecules has hampered this line of research. A combinatorial solution may be to encapsulate the cells within electrically active implants which can (i) improve cell survival; (ii) guide cell differentiation and (iii) stimulate growth factor production. To fabricate these implants, piezoceramic materials can be highly conformable, biocompatible and generate electrical activity in response to mechanical input (from body movement or non-invasive ultrasound stimulation). This study aims to investigate the use of piezoceramic substrates to encapsulate neural stem cells (NSCs; a major transplant population) and to examine any effect of the substrates on NSC regenerative behaviour.

Methods

KNN was embedded into polydimethyl siloxane (PDMS), a flexible biocompatible material, and underwent dielectrophoresis and poling to fabricate the piezoceramic substrate. NSCs were derived from the subventricular zone of p0-p3 mice, which were then seeded onto the KNN and cultured. We aim to examine cell viability (live/dead staining), proliferation (EdU incorporation) and differentiation (immunostaining) of NSCs grown on the KNN.

Approach for Statistical Analysis

Each experimental group will be compared against each other, using a one-way ANOVA along with a Bonferroni correction. The data will be derived from at least an n=3, where each n number is an individual experiment, having cells derived from separate biological litters of mice. Our preliminary data (n=2) suggests a trend of increased neurogenesis on positively charged and negatively charged poled KNN compared with unpoled KNN and glass coverslips (Fig 1).

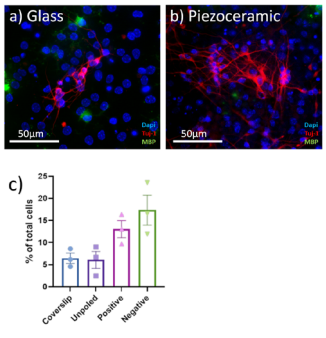

Figure a) Differentiated NSCs stained with Tuj-1 to detect neurons on glass coverslips. b) Differentiated NSCs stained with Tuj-1 to detect neurons on negatively poled KNN. c) Graph showing current quantification of the percentage of neurons derived from NSCs differentiated on different substrates.

Identification of molecular markers that correlate with the progression of Parkinson's Disease

Unique Code: PP001282

Authors: Llinos H Jones - Institute of Translational Medicine University of Liverpool, Luke D Marney - Institute of Translational Medicine University of Liverpool, John P Quinn - Department of Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology University of Liverpool, Vivien Jill Bubb - Department of Pharmacology and Therapeutics, Institute of Systems, Molecular and Integrative Biology University of Liverpool, Sulev Koks - Perron Institute for Neurological and Translational Science Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, Australia, Abigail L Pfaff - Perron Institute for Neurological and Translational Science Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Perth, Australia,

Topic: Disorders, treatments and translational neuroscience

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting 1% of the population over 60 years of age. PD pathology is characterised by the loss of dopaminergic neurons from the substantia nigra and the formation of neuronal inclusions called Lewy bodies. The development of PD involves a complex interaction of genetic and environmental factors. Many of the genetic factors affecting disease progression have been identified but there is much still to be determined. This is particularly true for those factors not causative of the disease, but progression and severity of the disease once diagnosed. We aim to address both genetic and transcriptomic changes which we can bioinformatically identify in the Parkinson's Progression Markers Initiative (PPMI) cohort which was established to identify PD progression markers to help understand disease aetiology and ultimately aid in the development of novel therapeutics.

Methods

Genetic data, longitudinal clinical data and transcriptomic data has been obtained from the Parkinson's Progression Markers Initiative (PPMI) cohort (www.ppmi-info.org). The DESeq2 package in R will be used to detect statistically significant differences in the gene expression profiles between the different genotypes which we are currently delineating to correlate with specific clinical progression markers. This will allow us to align genetic variation with blood transcriptomic changes with disease progression.

Approach for statistical analysis

Once we have identified targets using DESeq2, their association with PD progression will be analysed in the longitudinal analysis using a linear mixed-effects model combined with FDR correction, measuring the changes in phenotypic scores during follow-up visits that will later be analysed.

Neuroprotective role of Exogenous Oxytocin in Autistic-like Behavior, Brain Plasticity and Dopaminergic Signaling in Maternally Separated Mice Model

Unique Code: PP001308

Authors: PRATIBHA THAKUR - Bioscience Barkatullah University, Bhopal, India,

Topic: Disorders, treatments and translational neuroscience

Introduction: Early maternal separation influences the developing brain and possible onset of different neurodevelopment disorders like Autism Spectrum Disorder (ASD). ASD is characterized by persistent abnormalities in social interaction, behavior, mental development, and alteration of oxytocin receptor in the brain (Mansouri et al.,

2020). Study showed that early life experiences, like maternal separation are risk factor for ASD and abnormal signalling pathway in the developing brain causes dysfunction of the midbrain dopaminergic system (Pavăl, 2017).

Oxytocin is a neuropeptide hormone released by magnocellular neurons of the hypothalamus and has been previously to be proposed in the treatment of the pathogenesis of ASD by regulating social behavior (Donaldson and Young, 2008), eye contacts (Auyeung et al., 2015), and stereotypical behavior by the action of oxytocin receptor in hippocampus, striatum, nucleus accumbens, and amygdala (Green and Hollander, 2010; Lacivita et al., 2017) by modulating dopaminergic signalling pathways in various regions of the brain. Therefore, the aim of present study is to find the relationship between the onset of autistic like behavior & dopaminergic neuronal activity in the brain following by maternal separation and evaluate the possible effects of oxytocin treatments.

Method: Male mice will be exposed to the maternal separation from postnatal day (PND) 1 to PND14. After weaning the animal will be treated by intraperitoneal exposure of oxytocin (1mg/kg) (PND22-30). Autistic like behavior will be studied in adolescent stage (PND42-50), brain plasticity will be studied by stereotypical method and brain derived neurotrophic factor in plasma by using ELIZA. Immunohistochemical analysis of parasagittal brain section will be stained by tyrosine hydroxylase to mark the dopaminergic neuron and identify the effect of exogenous oxytocin on dopaminergic neuron.

Approach for statistical analysis: Images will be taken with confocal microscope with 20x and 63x oil immersion objectives analyzed by using NIH ImageJ software. Statistical analysis will involve the use of Two-way ANOVA to account for the difference between the groups. Tukey's post hoc test will be used to determine differences in the mean between pairs of groups.

Investigating the Cerebellar Potassium Channel Mechanisms of Schizophrenia

Unique Code: PP001339
Authors: Leah MacGregor - Health and Life Sciences De Montfort University, Lan Zhu - Health and Life Sciences De Montfort University
Topic: Disorders, treatments and translational neuroscience

Schizophrenia is a debilitating neuropsychiatric disorder with four symptom domains: positive, negative, affective and cognitive. Current antipsychotics face challenges such as treatment resistance and secondary cognitive symptoms [1].

The last 40 years have regarded the cerebellum as an integral node in neuronal circuits subserving all functional domains including cognition and emotion, in addition to motor-related functions. The past 20 years have seen cerebellar structural and functional abnormalities in schizophrenia [2].

Kv3 channels (Kv3.1-Kv3.4), a subfamily of voltage gated potassium channels, are involved in action potential repolarisation and enable neuron fast spiking. Kv3.1 contributes to cortical gamma oscillations in cortical GABAergic interneurons. Gamma oscillations are dysregulated in Kv3.1 knockout mice who show disrupted cognition and behaviour, which resembles schizophrenia symptoms. Kv3.1b expression is decreased in the cerebral cortex of schizophrenia patients. Kv3.1 and Kv3.3 are highly expressed in cerebellum [3].

This research aims to investigate 1) Kv3.1 and Kv3.3 regulation in the cerebellum of a phencyclidine mouse model of schizophrenia; 2) the possible alteration of electrophysiological behaviour of cerebellar cortical principle neuron Purkinje

cells; 3) the correlation between them.

Animal behaviour will be assessed to validate the mouse model. Western blot and immunohistochemistry will quantify and characterise proteins expression. In vivo single unit recording from mouse cerebellum will be analyse Purkinje cell firing properties including simple and complex spikes.

T-test/Mann-Whitney U test and ANOVA will be used to compare means of two and multiple groups, respectively.

References-
[1] Abel, T. and Nickl-Jockschat, T. (2016) The neurobiology of schizophrenia, San Diego, UNITED STATES: Elsevier Science & Technology.

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Searching for the missing link in Angelman Syndrome

Unique Code: PP001368
Authors: Felix Jozsa - Emergency Medicine Chelsea & Westminster Hospital
Topic: Disorders, treatments and translational neuroscience

Introduction
Angelman syndrome (AS) is a rare genetic disorder caused by loss of function of the maternal UBe3A allele on chromosome 15, resulting in a near total deficit of the CNS E3 ubiquitin ligase E6-AP (Sell, 2015). It is characterised clinically typically by seizures, microcephaly and developmental delay.

Calcium/calmodulin-dependent kinase II (CaMKII) is an abundant CNS kinase crucial to hippocampal long-term potentiation and memory. Key findings in hippocampal slices of the rodent AS model include hyperphosphorylated and dysfunctional CaMKII (Weeber, 2003). Experimental work showed rescue of LTP deficits in AS models possessing a further mutation blocking CaMKII hyperphosphorylation (van Woerden, 2007).

A substrate of E6-AP that regulates CaMKII phosphorylation is, therefore, a likely causative candidate for AS pathology. Adapting the previously posited UBe3A binding domain (UBD) (Greer, 2010), we have shown that the synaptic scaffolding protein Calcium/Cam associated serine kinase (CASK), which is known to regulate CaMKII phosphorylation (Malik, 2014), is a potential E6-AP substrate.

Methods
To assess the suppression of CASK expression by UBE3A in two-dimensional gel profiling. To assess the co-immunoprecipitation of these two proteins in vitro.

Approach for statistical Analysis
The primary outcome is to determine if E6-AP interacts with CASK in vitro. Proposed statistical analysis includes students t-testing comparing precipitation levels with controls.

Conclusion
This proposed intermediary between the E6-AP and CaMKII could serve as a future therapeutic target for this rare genetic disorder for which there is no current treatment. If confirmed, further experiments involving Angelman Syndrome mouse models with mutations inactivating CASK in vivo could be conducted to see if any rescue in behavioural deficits is observed.

Methods and technology development

Towards the design of a tetherless wearable device mounted on zebra finches' skulls to study experimental stuttering

Unique Code: PP001362
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Topic: Methods and technology development

Introduction:
Stuttering is a speech disorder characterized by prolongation of sounds, interruptions in speech, and repetition of words, sounds, or syllables. The songbird vocal system has emerged as the best-developed model for the neural basis of speech acquisition and production since songbirds are among the very few animals that learn their vocalizations through vocal imitation, like humans. Vocal control and learning are critically dependent on auditory feedback in both songbirds and humans. Continuous delayed auditory feedback (cDAF) is a technique that robustly disrupts speech fluency in normal humans and induces mild to severe forms of stuttering in songbirds. Researchers in the field expose songbirds to cDAF by implanting a piezoelectric accelerometer on the skull which records bone-conducted recordings that are uncontaminated by airborne sounds. Birds are usually tethered using a cable to an amplifier, and this process induces continuous discomfort to the tethered birds as they are not able to move freely inside the cage, thereby affecting their rate of song production and quality. In this work, we aim to develop a Bluetooth-enabled wearable device that can record, process, and transfer vocalization samples. The device would also enable wireless and programmatic manipulation of neuronal activities to induce cDAF variations and record the expected response. The device will be tested on adult zebra finches by using it to induce cDAF and look at changes and abnormalities in the song's temporal and spectral features post cDAF induction. The proposed project will lay the foundations for a better understanding of stuttering, vocal production and learning, and the effects of cDAF on them.

Methods:
The spectral and temporal features of the zebra finch birdsong are extracted using MATLAB to guide the hardware

design process. The prototype circuit is composed of three operating parts: a microcontroller, a Micro SD card module, and an accelerometer. The accelerometer sends data to the microcontroller, which saves it on an SD card. This data is then transmitted via Bluetooth to a mobile application and can be played back as cDAF via a microphone.

Statistical Methods:
Given that this is a hardware design project, statistical methods are not applicable.

Neurodevelopment and stem cells

Modelling the Role of PAX6 in Human Neural Induction Using Early Stage Cortical Organoids

Unique Code: PP001136
Authors: Helen Marshall - Centre for Discovery Brain Sciences The University of Edinburgh, Wai Kit Chan - Centre for Discovery Brain Sciences The University of Edinburgh, John O. Mason - Centre for Discovery Brain Sciences The University of Edinburgh, David Price - Centre for Discovery Brain Sciences The University of Edinburgh,
Topic: Neurodevelopment and stem cells

Introduction
PAX6 is a highly evolutionarily conserved transcription factor essential for healthy brain formation and exerts high-level control over cortical development (1). Mutations in PAX6 produce a wide range of conditions, the effects of which are often severe. PAX6 has been identified as a human neuroectoderm cell fate determinant (2), but its precise role in human neurodevelopment remains largely unstudied due to the practical and ethical limitations of investigating early embryonic events. In this project, early stage cortical organoids will be used to investigate these early processes in human cells. A combination of basic histology, 3D imaging and bulk RNA-sequencing will give insights into the roles of PAX6 during neural induction and also offer wider insights into neural organoid development.

Methods
PAX6 mutations have been induced in the NAS2 human induced pluripotent stem cell (hiPSC) background line using CRISPR/CAS9 gene editing to generate two mutant lines (A10, B2) and a second control line (CAS9_3). All four lines will be cultured in 3D under a feeder-free cortical organoid protocol and collected before and after the neural induction step. Samples will be used for bulk RNA sequencing and immunohistochemistry where they will be stained for neuroepithelial markers and imaged in 2D and 3D.

Approach for statistical analysis
Control and mutant organoid samples stained for neuroepithelial markers will be quantified and analysed using standard statistical methods. RNA-sequencing data will be used to perform differential gene expression analysis. To maximise statistical power, two mutant and two control lines will be used, in addition to a minimum of 3 replicated organoid batches from each line.

References:
(1) Yamashita, W., et al. Development, 2018;145
(2) Zhang, X., et al. Cell Stem Cell, 2010;7:90-100.

Cell-type specific effects of serotonin signalling on the development of cortical neurons in cell culture

Unique Code: PP001213

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Topic: Neurodevelopment and stem cells

Serotonin (5-HT) has been reported to affect neuronal growth during brain development, which we have previously analysed using rat cortical cell cultures. However, results between cultures were highly variable, which may reflect the heterogeneity of cortical cultures that consist of a variety of neuron types including principle pyramidal neurons and various types of mainly inhibitory interneurons. Similar variability in 5-HT effects on neurite growth are also apparent in other published studies using cortical and hippocampal cultures.

In order to address this issue and study whether 5-HT effects on neurite growth is cell type specific, we have started a project aimed at analysing dendrite growth of individual cortical neuron types in cell culture. For this purpose, cortical neurons from neonate rats (P1-2) are grown in Neurobasal/B27 Plus medium (Thermo-Fisher) and chronically treated with the 5HT1A/5HT7 receptor agonist 8-OH-DPAT (DPAT, 1 µM), the 5HT1A receptor antagonists WAY-100635 (WAY, 1 µM), the 5HT7 receptor antagonist SB 269970 (SB, 1 µM), DPAT+WAY or DPAT+SB. Cultures are fixed at 14 DIV and dendrites labelled using an anti-microtubule associate protein 2 antibody. Based on previous reports that cultured pyramidal neurons may retain some of their in vivo morphological features (Kriegstein & Dichter, 1983), we will attempt to classify cultured cortical neurons according to their morphology and compare this classification to the labelling with cell type specific markers CamKII (pyramidal neurons) and GAD65/67 (inhibitory interneurons). The correlation between the morphological and immunocytochemical classification will be analysed using Pearson's $\chi 2$ test. We will also compare the results of total neurite growth analysis with the results from analysing individual neurons. The ImageJ plugin Simple Neurite Tracer will be used to trace and analyse individual neurons, while a custom tool created in ImageJ will be used for the automatic measurement of total neurite growth across whole images. Statistical comparisons of neurite growth between treatment groups based on the analysis of growth across whole images and individual neurons will be carried out using linear mixed effects models (fixed factors: treatments, analysis type, random factors: cultures).

Control of axonal translation during neuronal development by 3'UTR isoforms of bifunctional transcripts

Unique Code: PP001229

Authors: Braulio Martinez - MRC-LMCB UCL

Topic: Neurodevelopment and stem cells

Background:
Neurons are highly specialised cells with complex morphologies which rely on the compartmentalisation of protein expression for growth and maintenance. Localisation and translation of specific mRNAs in response to external stimuli is a critical part of neuronal development to cope with relatively long distances between the transcription and translation machineries of neurons. In these compartments, defective RNA processing/RNA-binding proteins (RBPs) are principal causes of neurological disease, including Fragile X Syndrome. Our lab recently performed RNA sequencing of mRNA localised in axons and cell bodies of mouse sympathetic neurons and found that 3' UTR length greatly affected protein

expression levels. Furthermore, at least in the Tp53inp2 transcript, remodelling of the 3' UTR determined whether it would act in a coding-independent manner. These findings suggest a new class of bifunctional RNAs in which a transcript's 3' UTR may undergo remodelling and cleavage in axons. We hypothesise that the 3' UTR of bifunctional transcripts contains specific sequences which may be recognised by RBPs to initiate their remodelling, transport, and translation, ultimately controlling axonal development.

Methods:
Sympathetic neurons of a genetically modified mouse expressing HA-tagged 60S ribosomal subunits will be isolated and grown in compartmentalised cultures, which physically separate axons from cell bodies. After RNA purification of both compartments, Translating Ribosome Affinity Purification (TRAP) will be performed to isolate all actively translating mRNAs. TRAPed mRNAs will then undergo 3'-end sequencing and the resulting annotated data will be extensively analysed for splicing events, motifs, 3' UTR length, etc. Insights from this analysis will be used to design vectors with varying 3' UTR features and live image their effects on translation through SunTag.

Approach to Statistical Analysis:

All statistical tests will be conducted by HOMER software for sequencing data. Paired imaging data statistics will use a paired t-test performed in GraphPad Prism software.

Effects of early exposure to NMDA receptor NR1-specific antibodies on glutamate receptor expression and morphology in the developing mouse striatum

Unique Code: PP001270
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Topic: Neurodevelopment and stem cells

Introduction: Maternal antibodies cross the placenta in pregnancy to help establish the neonatal immune system. In this period, the blood-brain barrier is permeable, enabling antibodies to enter the brain. If antibodies are raised against certain receptors, they may alter neurodevelopment and have been implicated in disorders including autism, learning disabilities, and schizophrenia.

One target is the glutamatergic NMDA receptor (NMDAR). Some studies have shown these antibodies can be elevated in mothers of children with psychiatric disorders. Mechanistically, these antibodies are thought to cause receptor internalisation, leading to hypofunction, but little is known about specific brain circuits being disrupted. Patients with NMDA antibody-mediated disorders exhibit motor symptoms (among others), suggesting dysfunction of motor circuits including those of the basal ganglia.

Aim: To explore how early exposure to NMDA receptor antibodies, particularly against the NR1 subunit, affects glutamate receptor expression and morphology in the developing mouse basal ganglia, specifically the striatum.

Significance: This study will aid understanding of antibody-mediated mechanisms implicated in several neurodevelopmental disorders.

Methods: At embryonic day (E)14.5, pups will be injected intraventricularly in utero with patient derived NR1 specific- or control IgG. Brain tissue will be fixed at embryonic (E16.5) and early postnatal (P1-5) periods to coincide with the peaks of striatal neuro- and synaptogenesis. Tissue will be immunostained to allow quantification of proliferating cells, proliferative zone width, and cellular markers. qRT-PCR will be used to define expression of the target receptor (NMDA) and other glutamate receptors (e.g. AMPA) in dorsal and ventral regions in control and treated mice.

Statistical approach: There are two main outcomes. Firstly, a measure of potential morphological changes such as primordial striatum size. Secondly, a measure of changes in NR1 receptor expression. Normality will be assessed in each group using the Shapiro-Wilks test. Subunit expression will be compared using Student's t-tests (parametric data) or Wilcoxon signed-rank tests (non-parametric data). The same approach will be used for morphological data.

Neurons and glia: intrinsic properties, cell biology and cell types

Using organotypic brain slice cultures to assess microglia inflammasome activity in response to inflammatory stimuli in a mouse model of Down syndrome

Unique Code: PP001140

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Down syndrome (DS) is caused by trisomy of chromosome 21 (Hsa21) and is the leading genetic cause of Alzheimer's disease (AD) worldwide. Susceptibility to early-onset AD in DS is due to the location of the APP gene on Hsa21, resulting in high expression of APP and amyloid-β (Aβ) aggregation, however, other Hsa21 genes modulate AD pathology. Neuroinflammation contributes to AD in the general population. Recent studies show that neuroinflammation is altered in the brain of a juvenile mouse model of DS, and an activated microglial state occurs in the post-mortem brain of young adults with DS. Inflammasome activity is raised in tgAPP mouse models, in the post-mortem AD brain and IL-1β, a cytokine produced by inflammasomes, is raised in the DS brain. We hypothesize that IL-1β levels are raised in the DS brain, via upregulation of inflammasome activity. To test this hypothesis we will use organotypic hippocampal slice cultures (hOSCs) from a segmental duplication mouse model of DS to assess the response of microglia to inflammatory stimuli.

IL-1β abundance is raised in the cortex and hippocampus of the Dp1Tyb mouse model, which has an additional copy of 148 mouse orthologues for Hsa21 genes. Using the V-PLEX proinflammatory panel (MSD), I will determine the level of 10 inflammatory markers, including IL-1β, in 3-month cortex and hippocampus from Dp2Tyb, Dp3Tyb and Dp9Tyb mice (duplication of 36, 39 and 79 Hsa21 genes respectively), thus identifying a model with the smallest region of duplicated Hsa21 genes that raise IL-1β in the brain. I will then prepare hOSCs from P4-P7 pups from this DS model and WT control. hOSCs will be stimulated with agents shown to induce inflammasome activity, including LPS, ATP, oligomeric Aβ (or a combination of these) for 3, 6 and 12 hrs and compared to slices stimulated with vehicle. Inflammasome level and microglia activation state will be measured by quantifying ASC and active caspase-1 in IBA1+ microglia, using immunofluorescence, confocal microscopy and ImageJ analysis. IL-1β, IL-6 and TNFα cytokine levels in conditioned

culture media will be measured by ELISA and cytokine responses elicited by the stimuli will be compared between WT and DS models. Student's t-test and ANOVA statistical tests will be used to analyse the data.

Defining a new in vitro culture system to monitor the effects of glucose on microglial metabolism

Unique Code: PP001181

Authors: Lucrezia Bruno - School of Life Sciences Kingston university, Mike Stolinski - School of Life Sciences Kingston university, Francesca E Mackenzie - School of Life Sciences Kingston university,

Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Introduction Microglia play an important role in the early onset of Alzheimer's disease pathology1. They are responsible for maintaining brain homeostasis, where changes in energy metabolism alter microglial metabolic profile and function2. Defining a suitable in vitro culture system will allow investigation of microglial function within a simulated brain microenvironment. Previous studies have relied on growing microglia under optimal media conditions, not reflecting the brain's physiological levels of key metabolites. This study aims to define a suitable experimental culture system that reflects the brain's physiological glucose level, approximately 1mM3, so the effects of altered glucose concentration and other treatments can be tested.

Methods Most primary microglial studies use DMEM/F12 as culture medium4,5, as perhaps, being nutrient-rich, it better supports cell growth and proliferation. In our lab, growing SIM-A9 mouse microglial cells in this high glucose media showed optimal cell proliferation and viability. In physiological glucose (1mM) Neurobasal medium, SIM-A9 cells showed minimal cell proliferation but maintained their viability. However, to define this culture system further, the optimal time needed to maintain cells in 1mM glucose before inducing stress has to be determined. Cells will be initially grown in DMEM/F-12 medium (17.5mM glucose; Gibco, UK). At optimal confluence, cells will be re-seeded in Neurobasal medium with 1xB-27 supplement (Gibco, UK) at 1mM glucose. Medium glucose concentration will be measured every hour for 8 hours. Cellular glucose uptake will be detected by Glucose-Glo kit (Promega, UK). A microglial activation profile will also be obtained by qRT-PCR utilising expression of the pro-inflammatory markers TNFa, iNOS and Il-1b, and anti-inflammatory markers ARG-1 and MRC-1.

Statistical analysis Expression of microglial markers from cells in 1mM glucose will be compared to cells in high glucose using ANOVA.

References 1. Yoshiyama Y et al (2007) Neuron 53(3): 337-351. 2. Bernier L et al (2020) Trends in Neurosci 43(11):854-869. 3. Van de Ven K et al (2012) Diabetes 61. 4. Geric I et al (2019) Immunometabolism, 1. 5. Gao Y et al (2017) Cell Reports 20:3034–3042

Dissecting Fluoxetine Mechanisms on Astrocytic Lactate Release

Unique Code: PP001231

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Topic: Neurons and glia: intrinsic properties, cell biology and cell types

Depression is the most common mental health disorder, affecting over 300 million people worldwide. According to the monoaminergic theory, low levels of monoamines such as serotonin underlie depression. Antidepressants, including

specific serotonin transporter inhibitors (SSRIs), are the first line of treatment in depression. Their therapeutic effects are proposed to be mediated by an increase in brain serotonin levels due to inhibition of serotonin transporters. However, patients experience delayed symptom relief of 2 to 4- weeks, despite the instant rise in brain serotonin levels following SSRI treatment. Furthermore, in pre-clinical studies, therapeutic effects of SSRIs were found to be independent from brain serotonin levels.

Recent studies suggest that non-neuronal glial cells, including astrocytes, play an essential role in depression aetiology and might act as targets of SSRIs. In pre-clinical and clinical studies, SSRIs are able to reverse astrocyte depletion in brain areas essential for controlling emotions – the prefrontal cortex, hippocampus and amygdala. Astrocytes produce lactate, an energy substrate and a signalling molecule. Interestingly, SSRIs including fluoxetine can stimulate lactate release from cortical astrocyte cultures. However, SSRI-stimulated lactate production and release have not yet been fully investigated.

This study aims to quantify astrocytic lactate release following fluoxetine treatment and explore the underlying signalling pathways. First, we will quantify fluoxetine concentrations suitable for chronic treatment, of up to 7 days, in primary astrocyte cultures. Then within such non-toxic concentrations, we will establish the lowest fluoxetine concentration that triggers the most lactate release in primary astrocyte and brain slice cultures using fluorometric assay and voltammetry, respectively. Astrocyte mRNA will then be isolated to measure expression of genes related to mitochondrial function and ATP metabolism using RT-PCR. Independent t-tests or one-way ANOVA with post-hoc analysis will be employed to determine significance.

This study will provide a greater understanding of the underlying mechanisms of antidepressants on astrocytes that could potentially lead to identifying novel therapeutic targets in depression.

Psychiatry and mental health

Shifting towards a naturalistic paradigm to investigate dynamic emotional processing in the functional connectome in adolescent depression

Unique Code: PP001052

Authors: Jivesh Ramduny - Psychology Trinity College Dublin
Topic: Psychiatry and mental health

Introduction
Adolescence is a developmental period that is marked by significant brain plasticity and maturational change (Casey et al., 2008). This sensitive period is associated with increased vulnerability to emotional dysregulation and psychiatric symptoms related to depression, particularly amongst females (Fuhrmann et al., 2013). Recently, movie-watching fMRI has emerged as a promising naturalistic approach to examine the dynamics of emotional processing. Such paradigms have the potential to reveal processes supporting emotional regulation and dysregulation as they unfold. Here, we build on the work of Gruskin et al. (2020) to investigate dynamic patterns of emotional processing and regulation during an emotionally evocative movie, in neurotypical (NT) youths and adolescents suffering from depressive symptoms (DS). We hypothesise that dynamic emotional processing will be modulated by individual differences in both depressive symptom severity and emotional regulation.

Methods
Structural and functional imaging scans were obtained from 26 female DS adolescents (14-20 years) and 26 age- and gender-matched NT youths during which they watched an emotionally evocative movie ("The Present"). The Depressive Inventory from the Beck Youth Inventories (BYI-Dep; Beck et al., 1996) was used to assess the severity of depressive symptoms. Emotional regulation was assessed using the Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski et al., 2007). Data processing was performed using fMRIPrep in addition to confound regression (motion; WM/CSF; global signal). High-motion participants with mean framewise displacement over 0.3mm were excluded.

Approach for statistical analysis
Whole-brain functional connectome will be delineated using Shen parcellation. For each group, the pairwise similarity between each pair of participants will be computed to construct a 26x268 intersubject correlation (ISC) matrix. Hypothesis testing will be performed to examine the significance between the ISCs and behavioural scores using subject-wise bootstrapping. Nonparametric correlations will be computed over 10K times to obtain a null distribution. This procedure will be performed using a sliding window to capture moment-to-moment responses to emotional segments of the movie.

The Topology of Adversities in Adolescence

Unique Code: PP001343
Authors: Ayla Pollmann - Institute of Psychiatry, Psychology & Neuroscience King's College London
Topic: Psychiatry and mental health

Adverse events before the age of eighteen are common and include traumatic experiences ranging from sexual abuse to parental divorce. These stressful events have been linked to various physical and mental health issues. Previous research has focused mainly on childhood and adverse experiences in family environments. At the same time, initial evidence suggests that other types of adversity, such as bullying, may be particularly detrimental for adolescents. Compared with the body of work on adverse childhood experiences, however, there is little consensus about what types of adversity affect adolescents, which impedes the development of effective policies for prevention and intervention. I will characterise what types of adverse experiences affect adolescents, how these experiences co-occur, and their effect on mental health as well as on brain development and resilience factors later in life. My planned projects will provide actionable insights into mental health policy and practice.

Project 1: Psychopathology is complex, and there is a need to examine their interactions with potential antecedents, such as adversities. The first proposed study will address the question: Is there a difference in the types of adversity experienced in childhood and adolescence? How do different kinds of adverse experiences relate to mental health outcomes? I will use network analysis as a transdisciplinary method to answer these questions. In network analysis, variables are represented as nodes, while the relationships between variables are defined as lines or edges between the nodes. The centrality of a node signifies the relative importance of a node inside the network. I will be assessing centrality through measures such as betweenness, closeness and degree. An overview of the connective patterns among adversities will illustrate which adversities are closely related to each other in childhood compared to adolescence. I will access the individual relationships of adversities in childhood compared to adolescence with mental health outcomes in early adulthood. This knowledge will help to identify potential targets for future interventions.

Immune-system dysfunction across major psychiatric disorders

Unique Code: PP001344

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Topic: Psychiatry and mental health

Introduction

Immune-system dysfunction has been observed in major psychiatric disorders (major depressive disorder (MDD), schizophrenia (SZ), bipolar disorders (BP)). These disorders are highly heritable but heterogenous with overlapping genetic and environmental risk factors, symptoms, cognitive, neuroimaging and blood-based measures. This suggests multiple biological sub-types across conventional diagnostic boundaries. One potential stratification for major psychiatric disorders is an altered immune system.

Aim 1: Test if immune pathways are enriched in shared genetic factors across major psychiatric disorders.

Aim 2: Test if shared genetic factors across major psychiatric disorders associate with immune-related blood markers.

Methods

1. Conduct a genomic SEM common factor GWAS of SCZ, BD and MDD to derive genetic factors shared across disorders (Grotzinger et al, Nat. Hum. Behav., 2019) .

2. Conduct pathway analysis using MAGMA on common factor GWAS results (de Leeuw et al, PLoS Comput. Biol., 2015).

3. Create a cross-disorder PRS from the common factor GWAS results using PRSice-2 (Choi & O'Reilly, Gigascience, 2019) and test for associations with immune related blood markers (C-reactive protein and white blood cell counts) in UK Biobank participants (n=~300,000).

Statistical analysis

Genomic SEM common factor GWAS is conducted using the weighted least squares SEM model. Pathway analysis using MAGMA is conducted using windows of 35kb upstream and 10kb downstream around genes, annotated gene sets from MSigBD database (Liberzon et al, Bioinformatics, 2011) and a SNP wise mean model. GLM models used for associative testing will be conducted in R using the most appropriate distribution, link function and combination of covariates that produce normally distributed residuals.

Pharmacological characterizations of a new Ketamine derivative 2-oxo-PCMe

Unique Code: PP001399

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Topic: Psychiatry and mental health

Synthetic psychoactive substances (SPS) are novel drugs that have been designed with unique chemical structures that resemble naturally existing psychoactive substances. The popularity of SPS has exploded in recent decades and their therapeutic potential remains to be fully explored. However, misuse has been problematic as drug abuse legislature is evaded. The classic psychoactive drugs that SPS mimic include: Phyto-cannabinoids, psychostimulants, dissociative anaesthetics, sedative-hypnotics and hallucinogens. Despite their misuse, SPS have multiple actions on brain function and have demonstrated therapeutic potential in the treatment of epilepsy, depression and other neurodegenerative diseases (i.e., dementia). Recently, a new research molecule '2-oxo-PCMe' (a derivative of Ketamine, a N-methyl-D-aspartate receptor [NMDAR] antagonist) has become available and its effects on the brain remain unknown. The aim of this research is to study the effects of this new compound on excitatory glutamatergic transmission and synaptic plasticity mediated by NMDARs within the hippocampus.

The primary method used to investigate this hypothesis will be in-vitro electrophysiological recording in the hippocampal slice preparation. Briefly, a recording electrode will be placed in the stratum radiatum of the Hippocampal CA1 region and field excitatory post synaptic potentials (fEPSPs) will be evoked by electrical stimulation of Schaffer collateral commissural fibres. The NMDAR mediated component of fEPSPs will be isolated by the perfusion of drugs to block AMPA, GABAA and GABAB receptors. Under this condition the DE50 of 2-oxo-PCMe on NMDAR-mediated fEPSPs will be established.

Further experiments will explore the effects of 2-oxo-xxxe on the induction of NMDAR-mediated Long-term potentiation (LTP) and Long-term depression (LTD) at Hippocampal CA1 synapses. fEPSP peak amplitude will be analysed and t-tests will be utilised to assess statistical significance of the 2-oxo-PCMe effects on synaptic plasticity and ANOVA to analyse differences between concentration groups.

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Synapses and plasticity

Optogenetic mapping of the cellular specificity of the afferent inputs to the retrosplenial cortex

Unique Code: PP001047
Authors: Gabriella Margetts-Smith - College of Medicine and Health University of Exeter, Prof Andrew Randall - College of Medicine and Health University of Exeter (Associate), Dr Jonathan Witton - College of Medicine and Health University of Exeter, Prof John P. Aggleton - School of Psychology Cardiff University, Dr Michael T. Craig - Institute of Neuroscience and Psychology University of Glasgow,
Topic: Synapses and plasticity

One of the defining characteristics of the retrosplenial cortex (RSC) is the interconnectivity it shares with a range of distal brain regions. This connectivity could be critical to its role in learning and memory as reciprocal connections have been anatomically identified with other memory-associated regions such as the anterior cingulate cortex (ACC), the anterior thalamic nucleus (ATN) and the dorsal subiculum (dSub). However, the synaptic strength of these connections is still relatively unknown, therefore we are aiming to characterise and quantify the properties of the afferent pathways to

the RSC from these areas.

To achieve this we will optogenetically stimulate afferent terminals in the RSC in ex vivo murine slices following viral expression of channelrhodopsin2(H134R) in the target regions of the ACC, ATN and dSub. A whole-cell patch clamp electrophysiological technique will be used to perform voltage clamp recordings in pyramidal neurons in both the granular and dysgranular subregions of the RSC. Various stimulation train protocols will be applied to investigate potential differences in afferent strength and specificity, and post-hoc biocytin staining will be used to confirm neuronal identification, morphology and location.

Our analysis will include measurements of the generated EPSC/IPSC magnitude and kinetics, as well as paired pulse and AMPA/NMDA ratios, to provide a comprehensive description of the synaptic connectivity of these pathways onto RSC pyramidal neurons. We will use ANOVA to statistically compare data from the granular and dysgranular regions, further subdivided by laminar position, to identify variation in connectivity within the RSC itself for each afferent pathway. Analyses from different afferent pathways will be treat completely independently and not directly compared.

We expect to find that not all RSC afferent pathways are equal in strength, and provide an important addition to the standard neuroanatomical tracing of RSC connectivity since quantifying synaptic strength could potentially indicate the functionality of different pathways. Furthermore, characterisation of these pathways will provide a normal healthy baseline to compare against future research using disease models.

Other (teaching, history, outreach etc)

A Prospective Observational Cohort Study of Factors Influencing Trial Participation in People with Motor Neuron Disease (FIT-Participation-MND)

Unique Code: PP001075

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Topic: Other (teaching, history, outreach etc)

Introduction: Motor neuron disease (MND) is a rapidly progressive and fatal neurodegenerative disorder with limited treatment options. The Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial (MND-SMART) is a multi-site UK trial seeking to address the paucity in effective disease modifying drugs for people with MND (pwMND). Historically, neurological trials have been plagued by suboptimal recruitment and high rates of attrition. Failure to recruit and/or retain participants can cause insufficiently representative samples, terminated trials, or invalid conclusions. This study investigates patient-specific factors affecting recruitment and retention of pwMND to MND-SMART. Improved understanding of these factors may improve trial protocol design, optimise recruitment and retention.

Methods: PwMND on the Scottish MND Register, CARE-MND, will be invited to participate in a prospective observational cohort study that investigates factors affecting trial participation and attrition. We hypothesise that patient-specific factors will significantly affect trial recruitment and retention. Participants will complete the HADS, PHQ-9 and STAI-Y to evaluate neuropsychiatric symptoms, the ALSSQOL-20 and CDC-HQOL-4 for quality of life and a novel study-specific questionnaire on Attitudes towards Clinical Trial Participation (ACT-Q). Clinical data on phenotype, cognition (ECAS) and physical functioning (ALS-FRS(R)) will also be collated. Caregivers will complete the b-DAS apathy scale. After 12 months a data request to MND-SMART will evaluate recruitment and retention.

Analysis Plan: Descriptive statistics will summarise and compare assessments and participants reaching impairment thresholds. Variable groupings: attitudes, quality of life, cognition, behaviour, physical functioning, neuropsychiatric and phenotype. Univariate and multivariable logistic regression will explore association with participation/withdrawal in MND-SMART; presented as odds ratios and 95% confidence intervals.

Ethics: Ethical approval was provided by the West of Scotland Research Ethics Committee 3 (20/WS/0067) on 12th May 2020. The study is currently recruiting.

Census of neuroscientists and their ethnicity in the UK

Unique Code: PP001188
Authors: Dana Visnitchi - Student Placement British Neuroscience Association (BNA)
Topic: Other (teaching, history, outreach etc)

Introduction
In 2018 the British Neuroscience Association (BNA) conducted a project to obtain basic demographics on the number of neuroscientists in the UK, and their gender. A new census is now planned for 2021 to update the information collected in 2018 and, importantly, to add data about ethnicity. The goals of this project are to (1) enable the BNA to understand and represent the UK neuroscience population, and (2) obtain baseline numbers about the ethnic representation within UK neuroscience, which can be compared against the UK general population and against which progress towards improving representation in neuroscience can be measured.

Methods
Definitions are important to avoid ambiguity and collect data which can be directly compared with the 2018 census. In this project, the definitions from the previous 2018 census will be used for the following terms: ‘neuroscientist’, ‘postgraduate student’, ‘postgraduate course’, ‘neuroscience course’, ‘psychology (bio) course’, ‘psychology (social) course ’and ‘Neuroscience (optional) course’.

Student data: Using an updated list from the 2018’s census project of neuroscience and psychology courses from UK institutions, each institution will be contacted with a Freedom of Information (FOI) request for the number and ethnicity of students in each course.

Neuroscientist data: Search engines will be used to identify neuroscientists as far as possible via institution websites. This will then be checked with the BNA Local Group Representatives, a network of BNA groups across the UK.

General population data: This will be obtained from the Office for National Statistics (ONS).

All the data will be collected and held in compliance with the UK General Data Protection Regulation.

Analysis
Once the data is collected, the percentage of neuroscientists and students in each ethnic group will be compared to the percentages in the general population. To do so, two-way ANOVA tests will be performed. Afterwards, a post-hoc test – the Benjamini-Hochberg procedure - will be conducted to identify and prevent false positives.

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